US009102680B2

(12) **United States Patent**
Smolenskaya et al.

(10) **Patent No.: US 9,102,680 B2**
(45) **Date of Patent: Aug. 11, 2015**

(54) **CRYSTAL FORMS OF (R)-N-METHYLNALTREXONE BROMIDE AND USES THEREOF**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/682,878**

(22) Filed: **Nov. 21, 2012**

(65) **Prior Publication Data**

US 2014/0004188 A1 Jan. 2, 2014

Related U.S. Application Data

(63) Continuation of application No. 12/593,615, filed as application No. PCT/US2008/004116 on Mar. 28, 2008, now abandoned.

(60) Provisional application No. 60/921,111, filed on Mar. 29, 2007.

(51) **Int. Cl.**

C07D 471/00	(2006.01)
C07D 491/00	(2006.01)
C07D 498/00	(2006.01)
C07D 513/00	(2006.01)
C07D 515/00	(2006.01)
C07D 489/00	(2006.01)
A61K 31/44	(2006.01)
C07D 489/08	(2006.01)
C07D 489/04	(2006.01)
A61K 31/485	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 489/08*** (2013.01); ***A61K 31/485*** (2013.01); ***C07D 489/04*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides a new forms of (R)—N-methylnaltrexone, and compositions thereof, useful as a peripheral mu opioid receptor antagonist.

14 Claims, 10 Drawing Sheets

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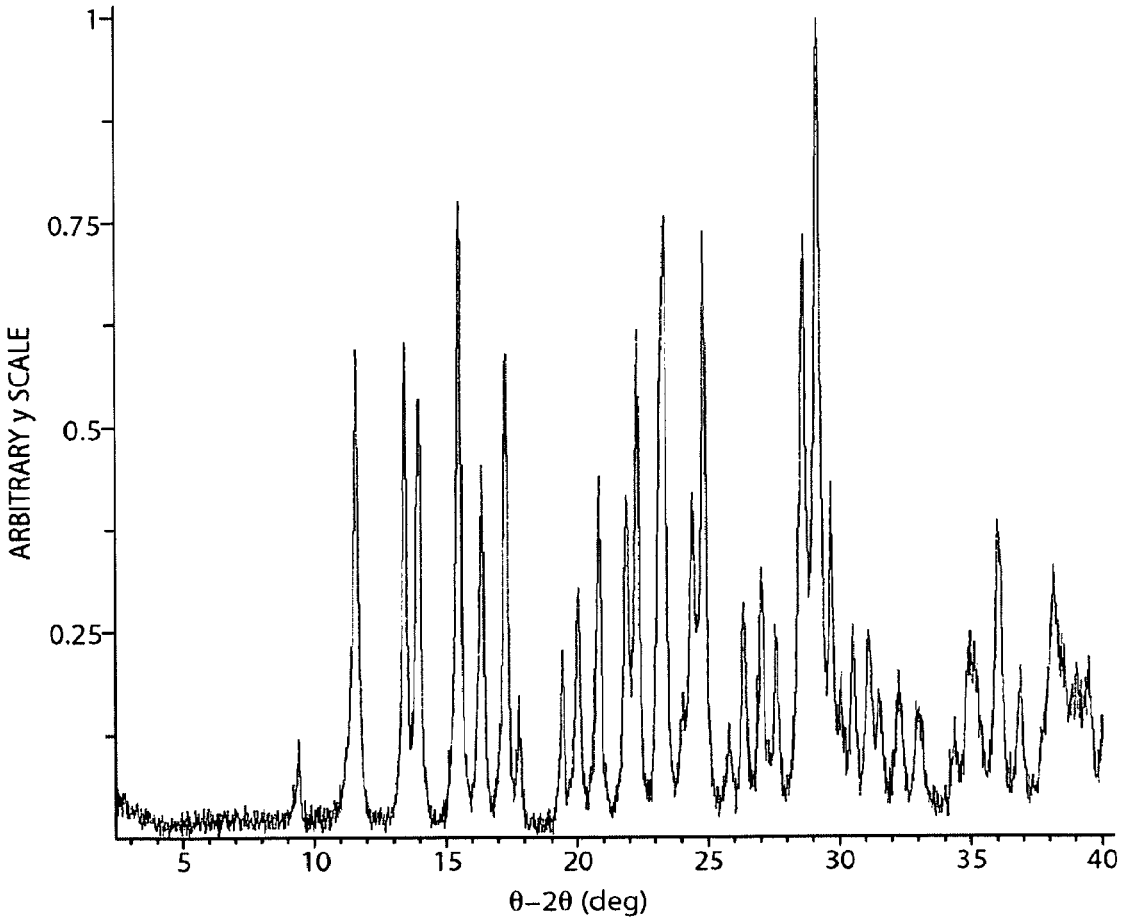


Fig. 1A

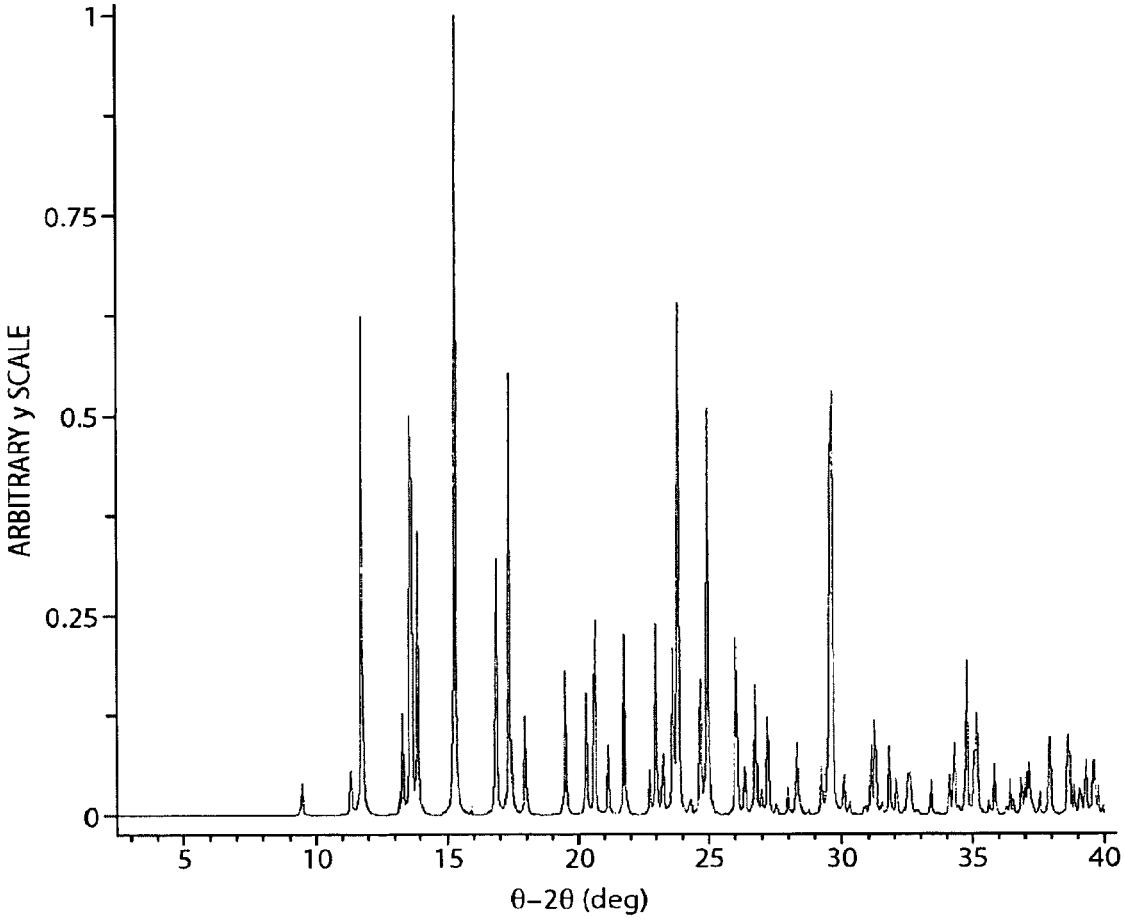


Fig. 1B

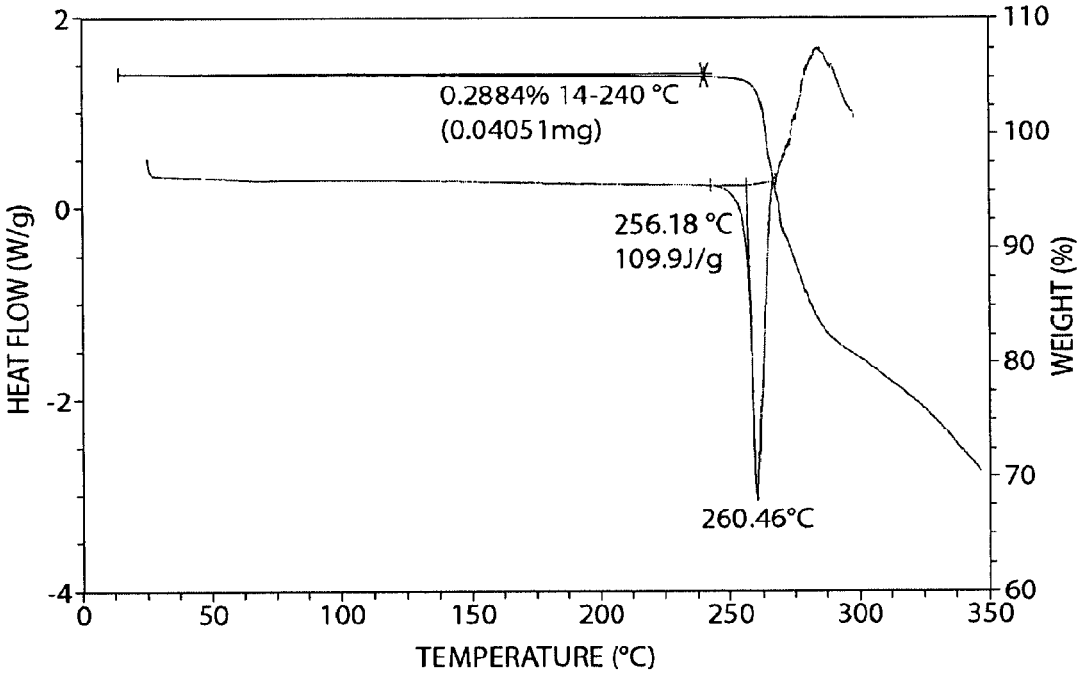

0.2884% 14-240 °C
(0.04051mg)
256.18 °C
109.9J/g
260.46°C
HEAT FLOW (W/g)
WEIGHT (%)
TEMPERATURE (°C)
2
0
-2
-4
110
100
90
80
70
60
0
50
100
150
200
250
300
350

Fig. 2

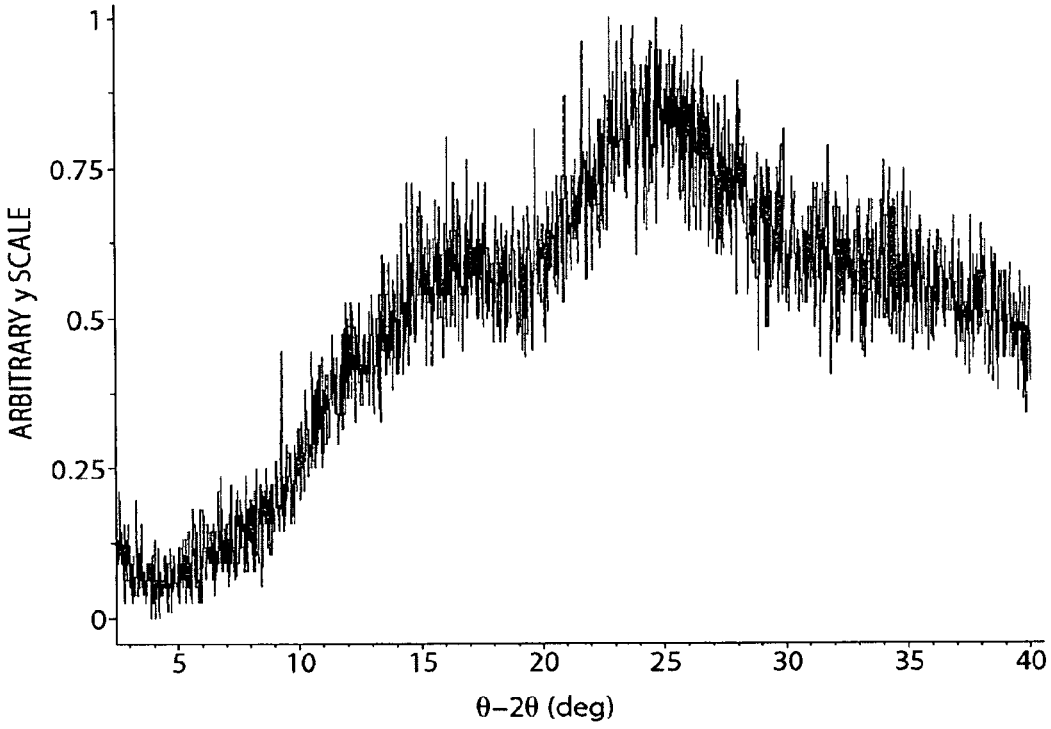


Fig. 3

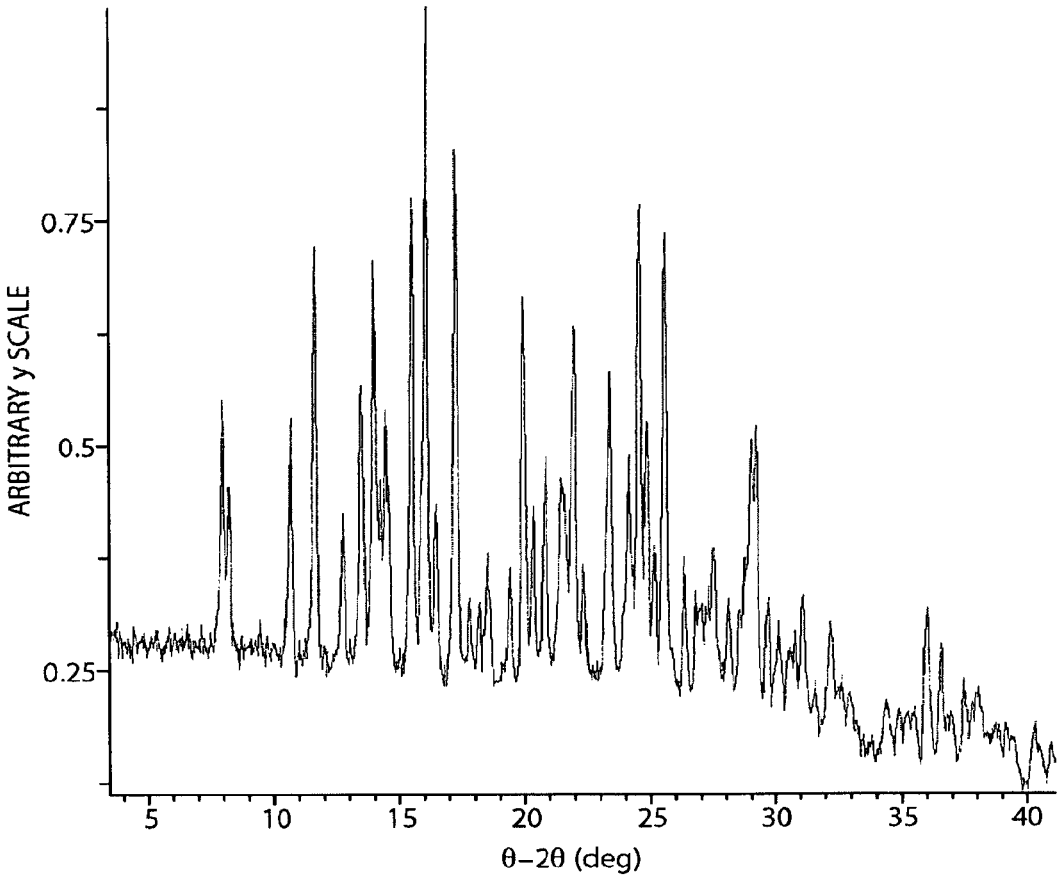


Fig. 4

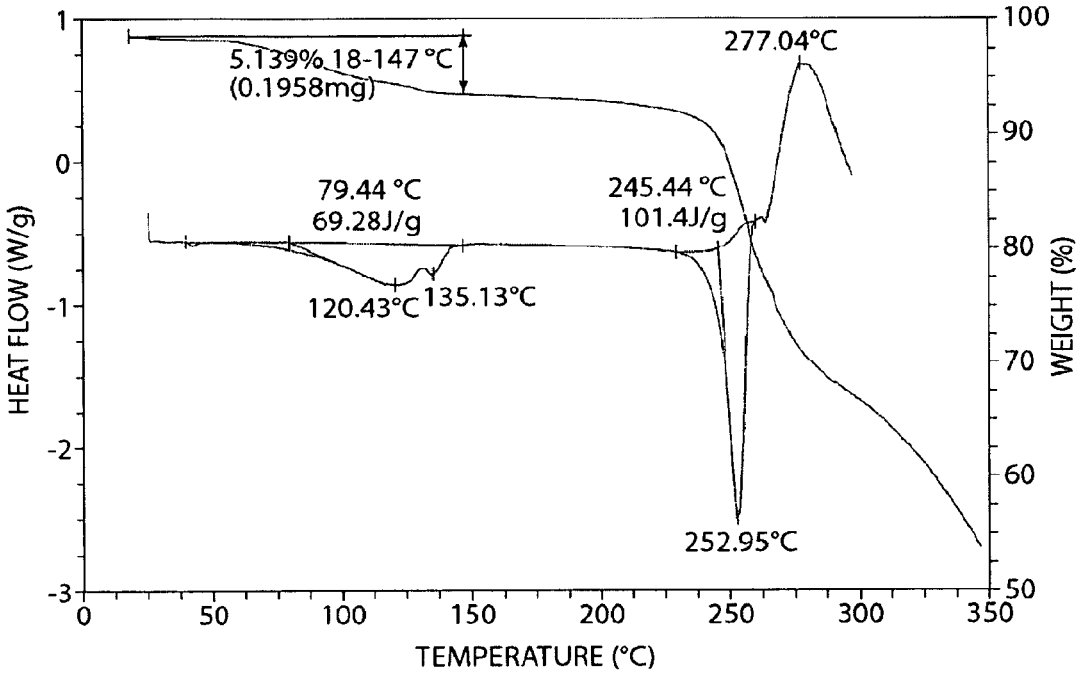

5.139% 18-147 °C
(0.1958mg)
277.04°C
79.44 °C
69.28J/g
245.44 °C
101.4J/g
120.43°C
135.13°C
252.95°C
HEAT FLOW (W/g)
WEIGHT (%)
TEMPERATURE (°C)
1
0
-1
-2
-3
100
90
80
70
60
50
0
50
100
150
200
250
300
350

Fig. 5

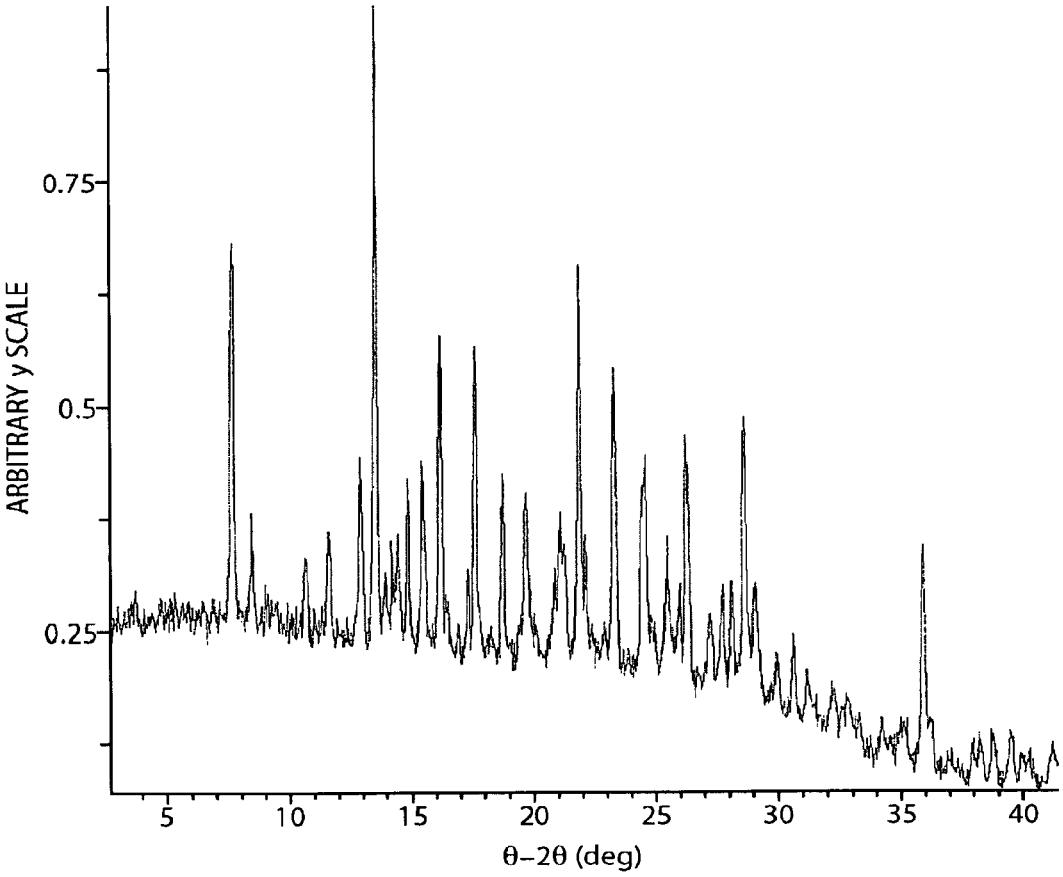


Fig. 6

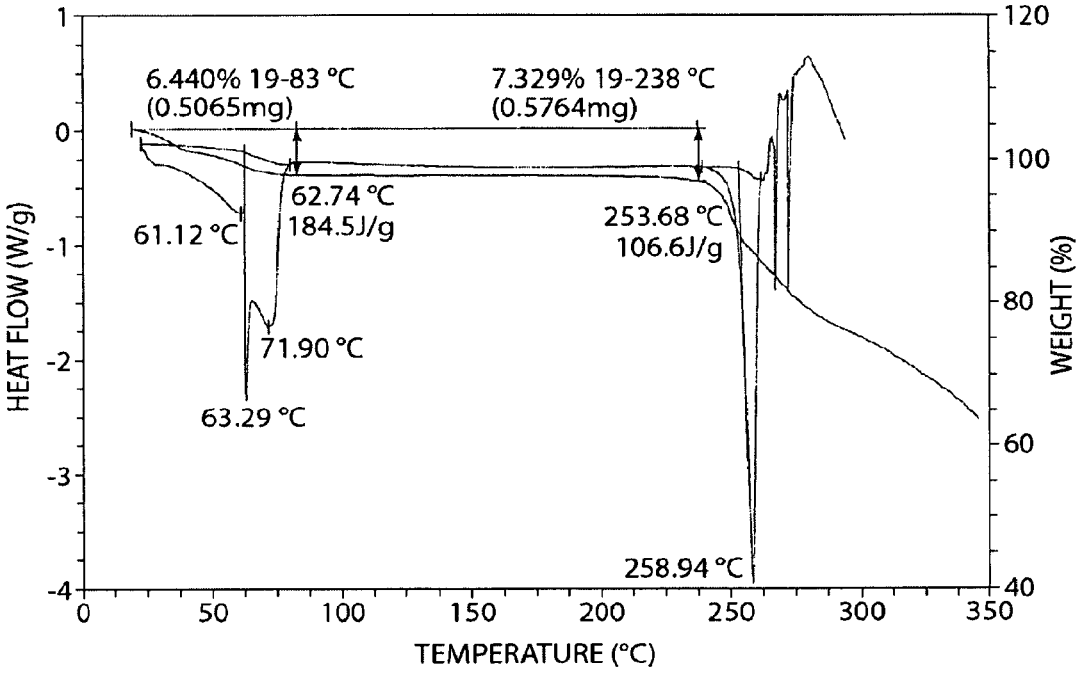

6.440% 19-83 °C
(0.5065mg)
7.329% 19-238 °C
(0.5764mg)
62.74 °C
184.5J/g
61.12 °C
253.68 °C
106.6J/g
71.90 °C
63.29 °C
258.94 °C
HEAT FLOW (W/g)
WEIGHT (%)
TEMPERATURE (°C)
1
0
-1
-2
-3
-4
120
100
80
60
40
0
50
100
150
200
250
300
350

Fig. 7

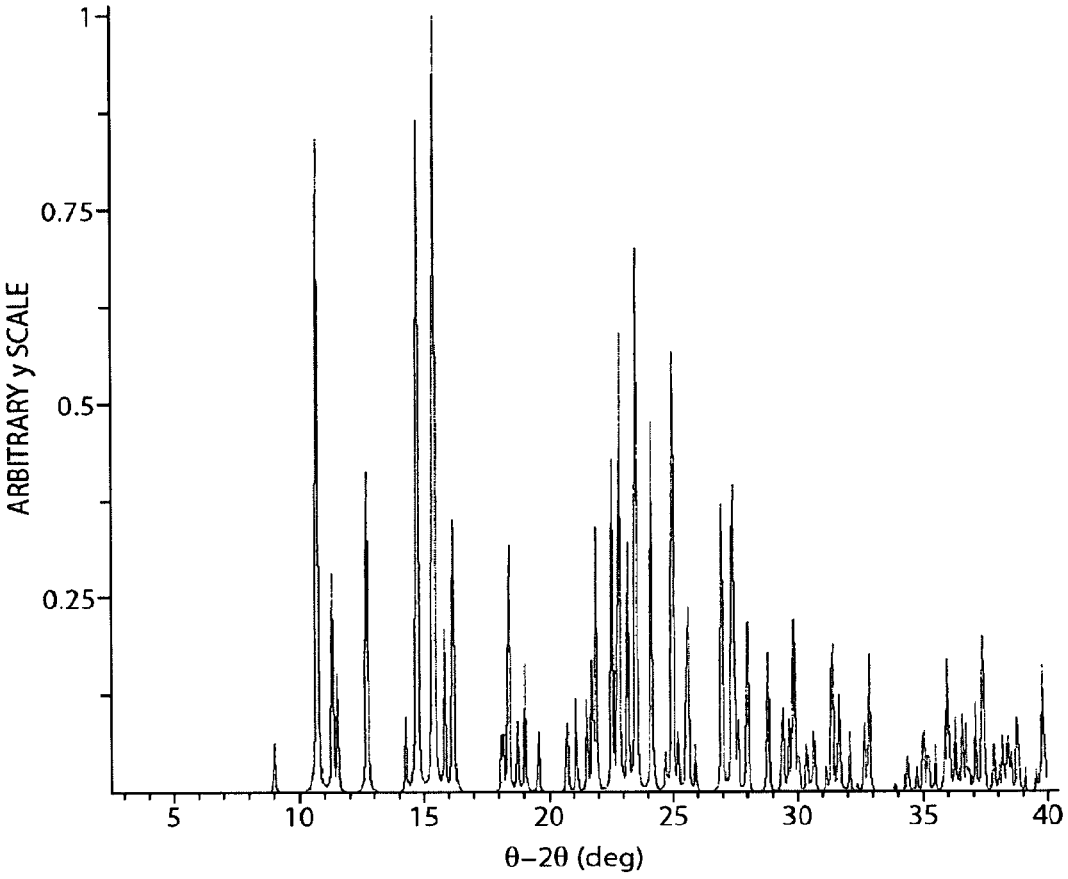


Fig. 8

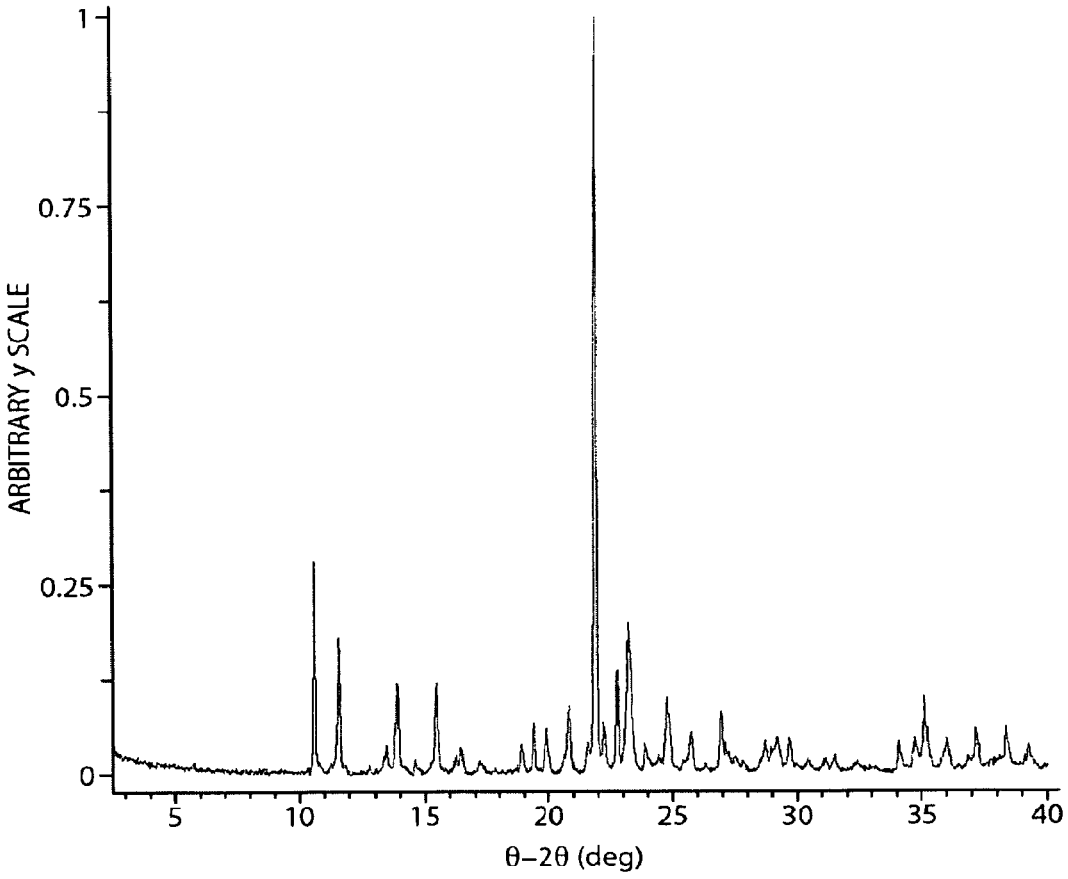


Fig. 9

CRYSTAL FORMS OF (R)-N-METHYLNALTREXONE BROMIDE AND USES THEREOF

RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 12/593,615, filed Aug. 12, 2010, which is a 35 U.S.C. §371 national stage filing of International Application No. PCT/US2008/004116, filed on Mar. 28, 2008, which claims priority to U.S. Provisional Patent Application No. 60/921,111, filed Mar. 29, 2007, the entirety of each of which applications are hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

Opioids are widely used in patients with advanced cancers and other terminal diseases to lessen suffering. Opioids are narcotic medications that activate opioid receptors located in the central nervous system to relieve pain. Opioids, however, also react with receptors outside of the central nervous system, resulting in side effects including constipation, nausea, vomiting, urinary retention, and severe itching. Most notable are the effects in the gastrointestinal tract (GI) where opioids inhibit gastric emptying and propulsive motor activity of the intestine, thereby decreasing the rate of intestinal transit and producing constipation. The effectiveness of opioids for pain is often limited due to resultant side effects, which can be debilitating and often cause patients to cease use of opioid analgesics.

In addition to analgesic opioid induced side effects, studies have suggested that endogenous opioid compounds and receptors may also affect activity of the gastrointestinal (GI) tract and may be involved in normal regulation of intestinal motility and mucosal transport of fluids in both animals and man, (Koch, T. R, et al, Digestive Diseases and Sciences 1991, 36, 712-728; Schuller, A. G. P., et al., Society of Neuroscience Abstracts 1998, 24, 524, Reisine, T., and Pasternak, G., Goodman & Gilman's The Pharmacological Basis of Therapeutics Ninth Edition 1996, 521-555 and Bagnol, D., et al., Regul. Pept. 1993, 47, 259-273). Thus, an abnormal physiological level of endogenous compounds and/or receptor activity may lead to bowel dysfunction.

For example, patients who have undergone surgical procedures, especially surgery of the abdomen, often suffer from a particular bowel dysfunction, called post-operative (or post-surgical) ileus, that may be caused by fluctuations in natural opioid levels. Similarly, women who have recently given birth commonly suffer from post-partum ileus, which is thought to be caused by similar natural opioid fluctuations as a result of birthing stress. Gastrointestinal dysfunction associated with post-operative or post partum ileus can typically last for 3 to 5 days, with some severe cases lasting more than a week. Administration of opioid analgesics to a patient after surgery, which is now an almost universal practice, may exacerbate bowel dysfunction, thereby delaying recovery of normal bowel function, prolonging hospital stays, and increasing medical care costs.

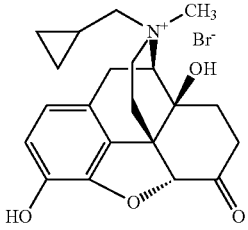
Opioid receptor antagonists such as naloxone, naltrexone, and nalmefene, have been studied as a means of antagonizing undesirable peripheral effects of opioids. However, these agents act not only on peripheral opioid receptors, but also on central nervous system sites, so that they sometimes reverse the beneficial analgesic effects of opioids, or cause symptoms of opioid withdrawal. Preferable approaches for use in controlling opioid-induced side effects include administration of peripheral opioid receptor antagonist compounds that do not readily cross the blood-brain barrier. For example, the peripheral μ opioid receptor antagonist compound methylnaltrexone and related compounds have been disclosed for use in curbing opioid-induced side effects in patients (e.g., constipation, pruritus, nausea, and/or vomiting). See, e.g., U.S. Pat. Nos. 5,972,954, 5,102,887, 4,861,781, and 4,719,215; and Yuan, C.-S. et al. Drug and Alcohol Dependence 1998, 52, 161. Similarly, peripherally selective piperidine-N-alkylcarboxylate and 3,4-dimethyl-4-aryl-piperidine opioid receptor antagonists have been described as being useful for treatment of opioid-induced side effects constipation, nausea or vomiting, as well as irritable bowel syndrome and idiopathic constipation. See, e.g., U.S. Pat. Nos. 5,250,542, 5,434,171, 5,159,081, and 5,270,328.

It would be desirable to provide peripheral μ opioid receptor antagonist compounds in a form suitable for administration to a patient in need of treatment for any of the above-mentioned disorders.

SUMMARY

The present invention provides solid forms of Compound 1, a peripheral μ opioid receptor antagonist:

1



where the compound is in the (R) configuration with respect to the nitrogen. The present invention also provides pharmaceutical compositions and formulations comprising such solid forms. Compound 1, and inventive solid forms thereof; is useful for the treatment, prevention, amelioration, delay or reduction of severity and/or incidence of side effects associated with opioid administration, such as, for example, gastrointestinal dysfunction (e.g., inhibition of intestinal motility, constipation, GI sphincter constriction, nausea, emesis (vomiting), biliary spasm, opioid bowel dysfunction, colic), dysphoria, pruritus, urinary retention, depression of respiration, papillary constriction, cardiovascular effects, chest wall rigidity and cough suppression, depression of stress response, and immune suppression associated with administration of narcotic analgesia, etc, or combinations thereof. Other uses of Compound 1, and inventive solid forms thereof as described herein, are set forth infra.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A depicts the X-Ray Powder Diffraction pattern for Form A.

FIG. **1**B depicts the X-Ray Powder Diffraction pattern for Form A, calculated for single crystal data collected at a temperature of 150±1 degrees K.

FIG. **2** depicts the DSC and TG overlay for Form A.

FIG. **3** depicts the X-Ray Powder Diffraction pattern for amorphous Compound 1.

FIG. **4** depicts the X-Ray Powder Diffraction pattern for Form B.

FIG. **5** depicts the DSC and TG overlay for Form B.

FIG. **6** depicts the X-Ray Powder Diffraction pattern for Form D.

FIG. **7** depicts the DSC and TG overlay for Form D.

FIG. **8** depicts the X-Ray Powder Diffraction pattern for Form C, calculated for single crystal data collected at a temperature of 150±1 degrees K.

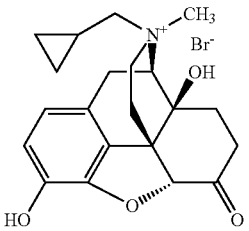
FIG. **9** depicts the X-Ray Powder Diffraction pattern for a mixture of Form A+Form C (preferred orientation).

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

General Description of Certain Aspects of the Invention

International patent application publication number WO2006/127899 describes Compound 1, (R)—N-methylnaltrexone bromide, which has the following structure;

1



where the compound is in the (R) configuration with respect to the nitrogen. In certain embodiments of the present invention, at least about 99.6%, 99.7%, 99.8%, 99.85%, 99.9%, or 99.95% of Compound 1 is in the (R) configuration with respect to nitrogen. Methods for determining the amount of (R)—N-methylnaltrexone bromide, present in a sample as compared to the amount of (S)—N-methylnaltrexone bromide present in that same sample, are described in detail in WO2006/127899, the entirety of which is hereby incorporated herein by reference. In other embodiments, Compound 1 contains 0.45% or less (S)—N-methylnaltrexone bromide. In still other embodiments, Compound 1 contains 0.30% or 0.05% or less (S)—N-methylnaltrexone bromide.

Compound 1, also known as "(R)-MNTX," exhibits peripheral μ opioid receptor antagonist activity in therapeutic models. Accordingly, Compound 1 is useful for antagonizing undesirable side effects of opioid activity, including those associated with opioid analgesic therapy (e.g., gastrointestinal effects (e.g., delayed gastric emptying, altered GI tract motility), etc.). In certain embodiments of the present invention, Compound 1 is useful for the treatment, prevention, amelioration, delay or reduction of severity and/or incidence of side effects associated with opioid administration, such as, for example, gastrointestinal dysfunction (e.g., inhibition of intestinal motility, constipation, GI sphincter constriction, nausea, emesis (vomiting), biliary spasm, opioid bowel dysfunction, colic), dysphoria, pruritus, urinary retention, depression of respiration, papillary constriction, cardiovascular effects, chest wall rigidity and cough suppression, depression of stress response, and immune suppression associated with administration of narcotic analgesia, etc, or combinations thereof. Other uses of Compound 1, and forms thereof as described herein, are set forth infra.

Solid Forms of Compound 1:

It has been found that Compound 1 can exist in a variety of solid forms. Such forms include neat crystal forms, known as polymorphs. Such solid forms also include solvates, hydrates, and amorphous. All such solid forms of Compound 1 are contemplated by the present invention. In certain embodiments, the present invention provides Compound 1 as a mixture of one or more solid forms selected from polymorphs, solvates, hydrates, and amorphous Compound 1.

As used herein, the term "polymorph" refers to different crystal structures achieved by a particular chemical entity. Specifically, polymorphs occur when a particular chemical compound can crystallize with more than one structural arrangement. As used herein, the term "solvate" refers to a crystal form where a stoichiometric or non-stoichiometric amount of solvent, or mixture of solvents, is incorporated into the crystal structure. Similarly, the term "hydrate" refers to a crystal form where a stoichiometric or non-stoichiometric amount of water is incorporated into the crystal structure.

In certain embodiments of the present invention, Compound 1 is provided as a crystalline solid, in some embodiments, the crystalline solid is substantially free of amorphous Compound 1. As used herein, the term "substantially free of amorphous Compound 1" means that the solid contains no significant amount of amorphous Compound 1. In certain embodiments of the present invention, the term "substantially free of amorphous Compound 1" means that at least about 95% by weight of Compound 1 in the solid is in crystalline form. In still other embodiments of the invention, the term "substantially free of amorphous Compound 1" means that at least about 99% by weight of Compound 1 in the solid is in crystalline form.

In certain embodiments of the present invention, Compound 1 is provided as a neat crystal form and thus does not have any water or solvent incorporated into the crystal structure. It has been found that Compound 1 can exist in at least one neat crystal form, or polymorph, referred to herein as Form A.

In certain embodiments, the present invention provides Form A of Compound 1. In other embodiments, the present invention provides Form A of Compound 1 characterized in that it has a peak in its X-ray powder diffraction ("XRPD") pattern at about 20.06 degrees 2-theta. As used herein, the term "about", when used in reference to any degree 2-theta value recited herein, refers to the stated value±0.2 degree 2-theta.

In certain embodiments, degree 2-theta values, as described herein, are reported with two decimal places. In other embodiments, degree 2-theta values, as described herein, are reported with one decimal place. In still other embodiments, degree 2-theta values, as described herein, are reported with no decimal places. It will be understood that where the term "about" is used in reference to any degree 2-theta value recited herein, this term refers to the stated value±0.2 degree 2-theta in accordance with the value's reported decimal place.

According to another embodiment, Form A of Compound 1 is characterized in that it has one or more peaks in its calculated XRPD pattern, for single crystal data collected at a temperature of 150±1° K, selected from those at about 116, 13.9, 16.85, 17.35, 23, 23.85, 24.7, 26.75, and 34.75 degrees 2-theta. In other embodiments, Form A of Compound 1 is characterized in that it has two or more, or three or more, peaks in its calculated XRPD pattern, for single crystal data collected at a temperature of 1.50±1° K selected from those at about 13.6, 13.9, 16.85, 17.35, 23, 23.85, 24.7, 26.75, and 34.75 degrees 2-theta. In still other embodiments, Form A of

Compound 1 is characterized in that it has substantially all of the peaks in its calculated XRPD pattern, for single crystal data collected at a temperature of 150±1° K, selected from those at about 13.6, 13.9, 16.85, 17.35, 23, 23.85, 24.7, 26.75, and 34.75 degrees 2-theta.

In other embodiments, Form A of Compound 1 is characterized in that is has substantially all of the peaks in its XRPD pattern listed in Table 1A, below.

TABLE 1A

XRPD Peaks for Form A Form A (°2θ)
11.56
13.44
13.98
15.52
16.4
17.3
19.42
20.06
20.82
21.9
22.3
23.34
24.42
24.84
26.38
27
27.64
28.62
29.16
29.7

In still other embodiments, Form A of Compound 1 is characterized in that it has substantially all of the peaks in its XRPD pattern listed in Table 1B, below.

TABLE 1B

XRPD Peaks for Form A	
Peak No.	°2θ
1	9.42
2	11.56
3	13.44
4	13.98
5	15.52
6	16.4
7	17.3
8	17.78
9	19.42
10	20.06
11	20.82
12	21.9
13	22.3
14	23.34
15	24.42
16	24.84
17	25.82
18	26.38
19	27
20	27.64
21	28.62
22	29.16
23	29.7
24	30.04
25	30.5
26	31.1
27	31.5
28	32.28
29	32.96
30	34.34
31	35.1
32	36
33	36.88

TABLE 1B-continued

XRPD Peaks for Form A	
Peak No.	°2θ
34	38.16
35	39.04
36	39.48

In certain embodiments of the present invention, Form A of Compound 1 is characterized in that it has substantially all of the peaks in its XRPD pattern, calculated from single crystal data collected at a temperature of 150±1° K, listed in Table 1C, below.

TABLE 1C

Calculated XRPD Peaks for a Single Crystal of Form A at 150 ± 1° K	
Peak No.	°2θ
1	9.5
2	11.35
3	11.75
4	13.3
5	13.6
6	13.9
7	15.3
8	16.85
9	17.35
10	17.95
11	19.5
12	20.3
13	20.65
14	21.15
15	21.8
16	22.75
17	23
18	23.3
19	23.65
20	23.85
21	24.7
22	24.95
23	26.05
24	26.35
25	26.75
26	27.2
27	28.35
28	29.25
29	29.65
30	30.1
31	31.1
32	31.25
33	31.8
34	32.05
35	32.55
36	33.4
37	34.3
38	34.75

According to one aspect, Form A of Compound 1 has an XRPD pattern substantially similar to that depicted in FIG. **1**A. As used herein, the phrase "substantially all of the peaks" means that the compound exhibits, in its XRPD, at least about 80% of the peaks listed. In other embodiments, the phrase "substantially all of the peaks" means that the compound exhibits, in its XRPD, at least about 85, 90, 95, 97, 98, or 99% of the peaks listed. According to other embodiments, Form A of Compound 1, has an XRPD pattern, calculated from single crystal data collected at a temperature of 150±1° K, substantially similar to that depicted in FIG. **1**B. In other embodiments, Form A is characterized in that it has a DSC pattern substantially similar to that depicted in FIG. **2**.

In certain embodiments of the invention, Form A is characterized by representative peaks in X-ray powder diffrac-

tion, which peaks are determined by comparison of X-ray diffraction pattern results for standard preparations of Form B, Form C, and Form D. In some embodiments, Form A is characterized by representative peaks in X-ray powder diffraction, which peaks are within the range of about 1 to about 30 degrees 2-theta, determined by comparison of X-ray diffraction pattern results for standard preparations of Form B, Form C, and Form D. Methods for preparing Form A of Compound 1 are described in the Examples section, infra.

According to another embodiment, the present invention provides Compound 1 as an amorphous solid. The X-ray powder diffraction pattern of amorphous Compound 1 is depicted in FIG. **3**. Amorphous solids are well known to one of ordinary skill in the art and are typically prepared by such methods as lyophilization, melting, and precipitation from supercritical fluid, among others. Methods of preparing amorphous Compound 1 are described in the Examples section, infra.

In certain embodiments, the present invention provides amorphous Compound 1 substantially free of crystalline Compound 1. As used herein, the term "substantially free of crystalline. Compound 1" means that the compound contains no significant amount of crystalline Compound 1. Crystalline Compound 1 includes neat crystal forms, solvates and hydrates as described herein or other crystalline forms of Compound 1 that may result from the preparation of, and/or isolation of, amorphous Compound 1. In certain embodiments of the present invention, at least about 95% by weight of Compound 1 present is amorphous Compound 1. In still other embodiments of the invention, at least about 99% by weight of Compound 1 present is amorphous Compound 1.

In other embodiments, the present invention provides a composition comprising amorphous Compound 1 and at least one crystalline form of Compound 1. Such crystalline forms of Compound 1 include neat crystal forms, solvates and hydrates as described herein or other crystalline forms of Compound 1 that may result from the preparation of and/or isolation of, amorphous Compound 1. In certain embodiments, the present invention provides a composition comprising amorphous Compound 1 and at least one crystalline form of Compound 1 as described herein. In other embodiments, the present invention provides a composition comprising amorphous Compound 1 and at least one crystalline form of Compound 1 selected from Form A, Form B, Form C, or Form D.

It has been found that Compound 1 can exist in at least two hydrate forms or mixed hydrate-solvate forms. Two such forms are referred to herein as Form B and Form D.

In certain embodiments, the present invention provides Form B of Compound 1. In certain embodiments, the present invention provides Form B of Compound 1, substantially free of other forms of Compound 1. In other embodiments, Form B is a mixed hydrate-methanolate of Compound 1. According to one embodiment, Form B is characterized in that it has one or more peaks in its XRPD pattern selected from those at about 7.9, 8.18, 20.3, 21.44, 24.11, and 25.12 degrees 2-theta. In certain embodiments, Form B is characterized in that it has two or more, or three or more, peaks in its XRPD pattern selected from those at about 7.9, 8.18, 20.3, 21.44, 24.11, and 25.12 degrees 2-theta. In other embodiments, Form B is characterized in that it has substantially all of the peaks in its XRPD pattern selected from those at about 7.9, 8.18, 20.3, 21.44, 24.11, and 25.12 degrees 2-theta.

In certain embodiments, Form B of Compound 1 is characterized in that is has substantially all of the peaks in its XRPD pattern listed in Table 2A, below.

TABLE 2A

XRPD Peaks for Form B Form B (°2θ)
7.9
8.18
10.64
11.57
12.68
13.44
13.89
14.38
15.42
16.01
16.39
17.18
19.89
20.79
21.44
21.9
23.35
24.49
24.87
25.53
29.17

In still other embodiments, Form B of Compound 1 is characterized in that is has substantially all of the peaks in its XRPD pattern listed in Table 2B, below.

TABLE 2B

XRPD Peaks for Form B	
Peak No.	°2θ
1	7.9
2	8.18
3	10.64
4	11.57
5	12.68
6	13.44
7	13.89
8	14.38
9	15.42
10	16.01
11	16.39
12	17.18
13	17.74
14	18.12
15	18.47
16	19.37
17	19.89
18	20.3
19	20.79
20	21.44
21	21.9
22	22.31
23	23.35
24	24.11
25	24.49
26	24.87
27	25.12
28	25.53
29	26.33
30	26.78
31	27.51
32	28.1
33	29.17
34	29.69
35	30.07
36	30.76
37	31.04
38	32.18
39	32.88
40	34.33

According to one aspect, Form B of Compound has an XRPD pattern substantially similar to that depicted in FIG. **4**.

In other embodiments, the present invention provides Form B of Compound 1 having a DSC pattern substantially similar to that depicted in FIG. **5**.

In certain embodiments of the invention, Form B is characterized by representative peaks in X-ray powder diffraction, which peaks are determined by comparison of X-ray diffraction pattern results for standard preparations of Form A, Form C, and Form D. In some embodiments, Form B is characterized by representative peaks in X-ray powder diffraction, which peaks are within the range of about 1 to about 30 degrees 2-theta, determined by comparison of X-ray diffraction pattern results for standard preparations of Form A, Form C, and Form D. Methods for preparing Form B of Compound 1 are described in the Examples section, infra.

In certain embodiments, the present invention provides Form D of Compound 1. In other embodiments, the present invention provides Form D of Compound 1, substantially free of other forms of Compound 1. According to one embodiment, Form D is characterized in that it has one or more peaks in its XRPD pattern selected from those at about 7.66, 8.42, 14.79, and 21.06 degrees 2-theta. In certain embodiments, Form D is characterized in that it has two or more, or three or more, peaks in its XRPD pattern selected from those at about 7.66, 8.42, 14.79, and 21.06 degrees 2-theta. In other embodiments, Form B is characterized in that it has substantially all of the peaks in its XRPD pattern selected from those at about 7.66, 8.42, 14.79, and 21.06 degrees 2-theta.

In certain embodiments, Form B of Compound 1 is characterized in that is has substantially all of the peaks in its XRPD pattern listed in Table 3A, below.

TABLE 3A

XRPD Peaks for Form D Form D (°2θ)
7.66
8.42
12.85
13.48
16.11
17.53
18.67
19.61
21.06
21.79
22.07
23.25
24.53
26.23

In still other embodiments, Form D of Compound 1 is characterized in that is has substantially all of the peaks in its XRPD pattern listed in Table 3B, below.

TABLE 3B

XRPD Peaks for Form D	
Peak No.	°2θ
1	7.66
2	8.42
3	9.43
4	10.6
5	11.57
6	12.85
7	13.48
8	13.89
9	14.17
10	14.38
11	14.79

TABLE 3B-continued

XRPD Peaks for Form D	
Peak No.	°2θ
12	15.38
13	16.11
14	17.22
15	17.53
16	18.67
17	19.61
18	20.79
19	21.06
20	21.79
21	22.07
22	23.25
23	24.53
24	25.43
25	25.91
26	26.23
27	27.2
28	27.71
29	28.06
30	28.55
31	29.03
32	29.86
33	30.56
34	31.11
35	32.22
36	32.7
37	34.12
38	34.89
39	35.82
40	37
41	37.86
42	38.11
43	38.63
44	39.46

According to one aspect, Form D of Compound 1 has an XRPD pattern substantially similar to that depicted in FIG. **6**. In other embodiments, the present invention provides Form D of Compound 1 having a DSC pattern substantially similar to that depicted in FIG. **7**.

In certain embodiments of the invention, Form D is characterized by representative peaks in X-ray powder diffraction, which peaks are determined by comparison of X-ray diffraction pattern results for standard preparations of Form A, Form B, and Form C. In some embodiments, Form D is characterized by representative peaks in X-ray powder diffraction, which peaks are within the range of about 1 to about 30 degrees 2-theta, determined by comparison of X-ray diffraction pattern results for standard preparations of Form A, Form B, and Form C. Methods for preparing Form D of Compound 1 are described in the Examples section, infra.

It has been found that Compound 1 can exist in solvated crystalline forms. In certain embodiments, the present invention provides a crystalline n-propanolate of Compound 1, referred to herein as Form C. In certain embodiments, the present invention provides Form C of Compound 1, substantially free of other forms of Compound 1. According to another embodiment, Form C of Compound 1 is characterized in that it has one or more peaks in its calculated MUD pattern, for single crystal data collected at a temperature of 150±1° K, selected from those at about 10.8, 12.8, 14.8, 15.9, 16.25, 18.5, 19.15, 22, 23.6, 24.25, 25.7, 27.5, 28.1, 28.9, 31.5, and 31.75 degrees 2-theta. In certain embodiments, Form C of Compound 1 is characterized in that it has two or more, or three or more, peaks in its calculated XRPD pattern, for single crystal data collected at a temperature of 150±1° K, selected from those at about 10.8, 12.8, 14.8, 15.9, 16.25, 18.5, 19.15, 22, 23.6, 24.25, 25.7, 27.5, 28.1, 28.9, 31.5, and 31.75 degrees 2-theta. In other embodiments, Form C of

Compound 1 is characterized in that it has substantially all of the peaks in its calculated XRPD pattern, for single crystal data collected at a temperature of 150±1° K, selected from those at about 10.8, 12.8, 14.8, 15.9, 16.25, 18.5, 19.15, 22, 23.6, 24.25, 25.7, 27.5, 28.1, 28.9, 31.5, and 31.75 degrees 2-theta.

In certain embodiments of the present invention, Form C of Compound 1 is characterized in that it has substantially all of the peaks in its XRPD pattern, calculated from single crystal data collected at a temperature of 150±1° K, listed in Table 4A, below.

TABLE 4A

XRPD Peaks Calculated for a Single Crystal of Form C at 150 ± 1° K

Peak No.	°2θ
1	9.1
2	10.8
3	11.4
4	11.6
5	12.8
6	14.35
7	14.8
8	15.5
9	15.9
10	16.25
11	18.25
12	18.5
13	18.85
14	19.15
15	19.7
16	20.85
17	21.2
18	21.65
19	21.85
20	22
21	22.65
22	22.95
23	23.3
24	23.6
25	24.25
26	25.05
27	25.3
28	25.7
29	26
30	27.05
31	27.5
32	28.1
33	28.9
34	29.5
35	29.9
36	30.45
37	30.75
38	31.5
39	31.75
40	32.15

In other embodiments, the present invention provides a composition comprising a mixture of Forms A and C of Compound 1. According to another embodiment, the XRPD pattern of the mixture of Forms A and C (preferred orientation) of Compound 1 has one or both peaks at about 10.58 and 22.74 degrees 2-theta. One of ordinary skill in the art will recognize that the designation of "preferred orientation" refers to a phenomenon that occurs when crystals have a tendency to align during the process of collecting XRPD data. This phenomenon often results in the formation of larger peaks in the XRPD pattern, as would be recognized by a skilled practitioner. In certain embodiments of the present invention, the XRPD pattern of the mixture of Forms A and C (preferred orientation) of Compound 1 has substantially all of the peaks at about 10.58, 11.56, 13.88, 15.42, 20.82, 21.86, 22.74, 23.2, 24.74, and 26.96 degrees 2-theta.

In other embodiments, the XRPD pattern of the mixture of Forms A and C (preferred orientation) of Compound 1 has substantially all of the peaks in its XRPD pattern listed in Table 4B, below.

TABLE 4B

XRPD Peaks for Forms A and C (preferred orientation)

Peak No.	°2θ
1	10.58
2	11.56
3	13.44
4	13.88
5	15.42
6	16.4
7	18.88
8	19.34
9	19.9
10	20.82
11	21.86
12	22.22
13	22.74
14	23.2
15	23.84
16	24.74
17	25.7
18	26.96
19	28.7
20	29.14
21	29.64
22	34.02
23	34.66
24	35.08
25	35.98
26	37.14
27	38.32
28	39.24

According to one aspect, Form C of Compound 1 has an XRPD pattern, calculated from single crystal data collected at a temperature of 150±1° K, substantially similar to that depicted in FIG. **8**. According to another aspect, a mixture of Forms A and C (preferred orientation) of Compound 1 has an XRPD pattern substantially similar to that depicted in FIG. **9**.

In certain embodiments of the invention, Form C is characterized by representative peaks in X-ray powder diffraction, which peaks are determined by comparison of X-ray diffraction pattern results for standard preparations of Form A, Form B, and Form D. In some embodiments, Form C is characterized by representative peaks in X-ray powder diffraction, which peaks are within the range of about 1 to about 30 degrees 2-theta, determined by comparison of X-ray diffraction pattern results for standard preparations of Form A, Form B, and Form D. Methods for preparing Form C of Compound 1 are described in the Examples section, infra.

In certain embodiments, the present invention provides Form A of Compound 1 comprising one or more additional solid forms of Compound 1. In other embodiments, the present invention provides Form A of Compound 1 comprising one or more of a hydrate of Compound 1, a solvate of Compound 1, or amorphous compound 2. In still other embodiments, the present invention provides Form A of Compound 1 comprising one or more of Form C, Form D, or amorphous, and optionally Form B. Thus, another aspect of the present invention provides a Compound 1 Composition.

As used herein, the term "Compound 1 Composition" refers to a composition comprising at least two of Form A, Form C, Form D, and amorphous Compound 1, and optionally Form B. In other embodiments, the Compound 1 Composition comprises at least two of Form B, Form C, Form F), and amorphous Compound 1. In certain embodiments of the

invention, the Compound 1. Composition comprises Form A of Compound 1 and Form D. In still other embodiments, the Compound 1 Composition comprises Form A and amorphous Compound 1.

Pharmaceutically Acceptable Compositions

As discussed above, the present invention provides new forms of Compound 1, which is useful as a peripheral mu opioid receptor antagonist and shows utility in clinically relevant models for treating opioid-induced side effects. According to another aspect of the present invention, pharmaceutically acceptable compositions are provided, comprising an inventive form of Compound 1, or a Compound 1 Composition, as described herein, and optionally comprising a pharmaceutically acceptable carrier, adjuvant, or vehicle. In certain embodiments of the present invention, such pharmaceutically acceptable compositions optionally further comprise one or more additional therapeutic agents.

As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with an inventive form of Compound 1, or Compound 1 Composition, of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

DEFINITIONS

As used herein, an "effective amount" of a compound or pharmaceutically acceptable composition can achieve a desired therapeutic and/or prophylactic effect. An "effective amount" is at least a minimal amount of a compound, or composition containing a compound, which is sufficient for preventing, ameliorating, reducing, delaying, or diminishing severity of one or more symptoms of a disorder associated with modulation of peripheral μ opioid receptors, and/or for preventing, ameliorating, delaying or diminishing severity of side effects associated with opioid analgesic therapy (e.g., gastrointestinal dysfunction (e.g., dysmotility constipation, etc.), nausea, emesis, (e.g., nausea), etc.). An "effective amount" of a compound, or composition containing a compound, is sufficient for prevention, amelioration, reduction, delay or a decrease in the symptoms associated with, a disease associated with aberrant endogenous peripheral opioid or μ opioid receptor activity (e.g., idiopathic constipation, ileus, etc.).

The term "formulation" refers to a preparation that includes an inventive form of Compound 1, or Compound 1 Composition, in combination with one or more excipients for administration to a subject. In general, particular pharmaceutical additives are selected with the aim of enabling an optimal release, distribution and development of activity of an inventive form of Compound 1, or Compound 1 Composition, for the respective applications.

The term "subject", as used herein, means a mammal and includes human and animal subjects, such as domestic animals (e.g., horses, dogs, cats, etc.).

The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated.

An inventive form of Compound 1, or Compound 1 Composition, according to the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a disorder associated with modulation of peripheral μ opioid receptors. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. It will be understood, however, that the total daily usage of an inventive form of Compound 1, or Compound 1 Composition, will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, nasally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or the like, depending on the severity of the infection being treated. In certain embodiments, an inventive form of Compound 1, or Compound 1 Composition, may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

Liquid dosage forms for oral or nasal administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, aerosols,

gels, syrups, and elixirs. In addition to an inventive form of Compound 1, or Compound 1 Composition, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a pharmaceutically acceptable propellant. The aerosol dosage forms can also take the form of a pump-atomiser.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

Advantageously, amorphous Compound 1, as described herein, has enhanced water solubility. Accordingly, amorphous Compound 1 is useful for intravascular and intramuscular delivery. In certain embodiments, the present invention also relates to an injectable formulation for intravascular or intramuscular delivery.

In order to prolong the effect of an inventive form of Compound 1, or Compound 1 Composition, of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly (orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

Typical parenteral compositions consist of a solution or suspension of the compound in a sterile aqueous carrier or non-aqueous or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for rectal or vaginal administration are conveniently in the form of suppositories, pessaries, vaginal tabs, foams, or enemas. Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing an inventive form of Compound 1, or Compound 1 Composition, with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, an inventive form of Compound 1, or Compound 1 Composition, is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium salts, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

An inventive form of Compound 1, or Compound 1 Composition, can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared

with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms an inventive form of Compound 1, or Compound 1 Composition, may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the ease of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Compositions for oral administration may be designed to protect the active ingredient against degradation as it passes through the alimentary tract, for example by an outer coating of the formulation on a tablet or capsule.

In another embodiment, an inventive form of Compound 1, or Compound 1 Composition, is be provided in an extended (or "delayed" or "sustained") release composition. This delayed release composition comprises an inventive form of Compound 1, or Compound 1 Composition, in combination with a delayed release component. This composition allows targeted release of an inventive form of Compound 1, or Compound 1 Composition, into the lower gastrointestinal tract; for example into the small intestine, the large intestine, the colon and/or the rectum. In certain embodiments, the delayed release composition comprising an inventive form of Compound 1, or Compound 1 Composition, further comprises an enteric or pH dependent coating such as cellulose acetate phthalates and other phthalates (e.g. polyvinyl acetate phthalate, methacrylates (Eudragits)). Alternatively, the delayed release composition provides controlled release to the small intestine and/or colon by the provision of pH sensitive methacrylate coatings, pH sensitive polymeric microspheres, or polymers which undergo degradation by hydrolysis. The delayed release composition can be formulated with hydrophobic or gelling excipients or coatings. Colonic delivery can further be provided by coatings which are digested by bacterial enzymes such as amylose or pectin, by pH dependent polymers, by hydrogel plugs swelling with time (Pulsincap), by time dependent hydrogel coatings and/or by acrylic acid linked to azoaromatic bonds coatings.

In certain embodiments, the delayed release compositions of the present invention comprise hypromellose, microcrystalline cellulose, and a lubricant. The mixture of an inventive form of Compound 1, or Compound 1 Composition, hypromellose and microcrystalline cellulose may be formulated into a tablet or capsule for oral administration, in certain embodiments, the mixture is granulated and pressed into tablets.

In other embodiments, the delayed release compositions of the present invention are provided in a multiparticulate formulation. A mixture of an inventive form of Compound 1, or Compound 1 Composition, and a suitable polymer is granulated to form pellets which are coated. In certain embodiments, the pellets are seal coated with a non-functional coating. In other embodiments, the pellets are first seal coated with a non-functional coating and then coated with a functional coating.

As used herein the term "non-functional coating" is a coating that does not effect the release rate of the drug. Examples of a non-functional coat include hydroxypropyl cellulose, hypromellose or polyvinyl alcohol. In certain embodiments, the non-functional coating is Opadry® Clear, which contains, hydroxypropyl methylcellulose and polyethylene glycol.

As used herein, the term "functional coating" is a coating that affects the release rate of the drug from the dosage form. Examples of a functional coating include ethylcellulose and polymethacrylate derivatives (Eudragits).

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any deeded preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

The compositions may contain from 0.1% to 99% (w/w) preferably from 0.1-60% (w/w), more preferably 0.2-20% by weight and most preferably 0.25 to 12% (w/w) of an inventive form of Compound 1, or Compound 1 Composition, depending on the method of administration.

Combination Products and Combined Administration

In certain embodiments, an inventive form of Compound 1, or Compound 1 Composition, may be administered alone to treat one or more disorders as described herein, or alternatively may be administered in combination with (whether simultaneously or sequentially) one or more other active agents useful to treat one or more disorders as described herein. Thus, an inventive composition, or formulation thereof, can be administered concurrently with, prior to, or subsequent to, one or inure active agents.

In certain embodiments, inventive compositions include one or more other active agents in addition to an inventive form of Compound 1, or Compound/Composition, that is not an inventive form of Compound 1, or Compound 1 Composition. In certain embodiments, the present invention provides a formulation that delivers an inventive form of Compound 1, or Compound 1 Composition, and at least one additional active agent.

In some embodiments, inventive formulations comprise both an opioid and an inventive form of Compound 1, or Compound 1. Composition. Such combination products, containing both an opioid and an inventive form of Compound 1, or Compound 1 Composition, would allow simultaneous relief of pain and minimization of opioid-associated side effects (e.g., gastrointestinal effects (e.g., delayed gastric emptying, altered GI tract motility), etc.).

Opioids useful in treatment of analgesia are known in the art. For example, opioid compounds include, but are not limited to, alfentanil, anileridine, asimadoline, bremazocine, buprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, ethylmorphine, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, nicomorphine, opium, oxycodone, oxymorphone, papaveretum, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, and tramadol. In some embodiments the opioid is at least one opioid selected from

alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, nicomorphine, oxycodone, oxymorphone, papaveretum, pentazocine, propiram, propoxyphene, sufentanil and/or tramadol. In certain embodiments of the present invention, the opioid is selected from morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl, tramadol, and mixtures thereof. In a particular embodiment, the opioid is loperamide. In other embodiments, the opioid is a mixed agonist such as butorphanol. In some embodiments, the subjects are administered inure than one opioid, for example, morphine and heroin or methadone and heroin.

The amount of additional active agents) present in combination compositions of this invention will typically be no more than the amount that would normally be administered in a composition comprising that active agent as the only therapeutic agent. In certain embodiments of the present invention, the amount of additional active agent will range from about 50% to 100% of the amount normally present in a composition comprising that compound as the only therapeutic agent.

In certain embodiments, inventive formulations may also be used in conjunction with and/or in combination with conventional therapies for gastrointestinal dysfunction to aid in the amelioration of constipation and bowel dysfunction. For example, conventional therapies include, but may not be limited to functional stimulation of the intestinal tract, stool softening agents, laxatives (e.g., diphelymethane laxatives, cathartic laxatives, osmotic laxatives, saline laxatives, etc), bulk forming agents and laxatives, lubricants, intravenous hydration, and nasogastric decompression.

Uses and Kits of Inventive Formulations

As discussed above, the present invention provides inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, useful in antagonizing undesirable side effects of opioid analgesic therapy (e.g., gastrointestinal effects (e.g., delayed gastric emptying, altered GI tract motility), etc.). Furthermore, inventive forms of Compound 1, or a Compound 1 Composition, and pharmaceutically acceptable compositions and formulations thereof, may be used as to treat subjects having disease states that are ameliorated by binding μ opioid receptors, or in any treatment wherein temporary suppression of the μ opioid receptor system is desired (e.g., ileus, etc.). In certain embodiments of the present invention, methods of use of formulations are in human subjects.

Accordingly, administration of an inventive form of Compound 1, or a Compound 1 Composition, or a pharmaceutically acceptable composition or formulation thereof, may be advantageous for treatment, prevention, amelioration, delay or reduction of side effects of opioid use, such as, for example, gastrointestinal dysfunction (e.g., inhibition of intestinal motility, constipation, GI sphincter constriction, nausea, emesis (vomiting), biliary spasm, opioid bowel dysfunction, colic, dysphoria, pruritus, urinary retention, depression of respiration, papillary constriction, cardiovascular effects, chest wall rigidity and cough suppression, depression of stress response, and immune suppression associated with use of narcotic analgesia, etc, or combinations thereof. Use of an inventive form of Compound 1, or a Compound 1 Composition, or a pharmaceutically acceptable composition or formulation thereof, may thus be beneficial from a quality of life standpoint for subjects receiving opioids, as well as to reduce complications arising from chronic constipation, such as hemorrhoids, appetite suppression, mucosal breakdown, sepsis, colon cancer risk, and myocardial infarction.

In some embodiments, inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, are useful for administration to a subject receiving acute opioid administration, in some embodiments, provided formulations are useful for administration to patients suffering from post-operative gastrointestinal dysfunction.

In other embodiments, inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, are also useful for administration to subjects receiving chronic opioid administration (e.g., terminally ill patients receiving opioid therapy such as an AIDS patient, a cancer patient, a cardiovascular patient; subjects receiving chronic opioid therapy for pain management; subjects receiving opioid therapy for maintenance of opioid withdrawal). In some embodiments, the subject is a subject using opioid for chronic pain management. In some embodiments, the subject is a terminally ill patient. In other embodiments the subject is a person receiving opioid withdrawal maintenance therapy.

Alternative or additional uses for inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, described herein may be to treat, reduce, inhibit, or prevent effects of opioid use including, e.g., aberrant migration or proliferation of endothelial cells (e.g., vascular endothelial cells), increased angiogenesis, and increase in lethal factor production from opportunistic infectious agents (e.g., *Pseudomonas aeruginosa*). Additional advantageous uses of inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, include treatment of opioid-induced immune suppression, inhibition of angiogenesis, inhibition of vascular proliferation, treatment of pain, treatment of inflammatory conditions such as inflammatory bowel syndrome, treatment of infectious diseases and diseases of the musculoskeletal system such as osteoporosis, arthritis, osteitis, periostitis, myopathies, and treatment of autoimmune diseases.

In certain embodiments, inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, of the invention may be used in methods for preventing, inhibiting, reducing, delaying, diminishing or treating gastrointestinal dysfunction, including, but not limited to, irritable bowel syndrome, opioid-induced bowel dysfunction, colitis, post-operative or postpartum ileus, nausea and/or vomiting, decreased gastric motility and emptying, inhibition of the stomach, and small and/or large intestinal propulsion, increased amplitude of non-propulsive segmental contractions, constriction of sphincter of Oddi, increased anal sphincter tone, impaired reflex relaxation with rectal distention, diminished gastric, biliary, pancreatic or intestinal secretions, increased absorption of water from bowel contents, gastro-esophageal reflux, gastroparesis, cramping, bloating, abdominal or epigastric pain and discomfort, constipation, idiopathic constipation, post-operative gastrointestinal dysfunction following abdominal surgery (e.g., colectomy (e.g., right hemicolectomy, left hemicolectomy, transverse hemicolectomy, colectomy takedown, low anterior resection)), and delayed absorption of orally administered medications or nutritive substances.

Provided forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, are also useful in treatment of conditions including cancers involving angiogenesis, immune suppression, sickle cell anemia, vascular wounds, and retinopa-

thy, treatment of inflammation associated disorders (e.g., irritable bowel syndrome), immune suppression, chronic inflammation.

In still further embodiments, veterinary applications (e.g., treatment of domestic animals, e.g. horse, dogs, cats, etc.) of use of inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, are provided. Thus, use of provided formulations in veterinary applications analogous to those discussed above for human subjects is contemplated. For example, inhibition of equine gastrointestinal motility, such as colic and constipation, may be fatal to a horse. Resulting pain suffered by the horse with colic can result in a death-inducing shock, while a long-term case of constipation may also cause a horse's death. Treatment of equines with peripheral opioid receptor antagonists has been described, e.g., in U.S. Patent Publication No. 20050124657 published Jan. 20, 2005.

It will also be appreciated that inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, can be employed in combination therapies, that is, inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. Particular combination therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that therapies employed may achieve a desired effect for the same disorder (for example, a formulation may be administered concurrently with another compound used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic compounds which are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

In other embodiments, inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, and unit dose forms are useful in preparation of medicaments, including, but not limited to medicaments useful in the treatment of side effects of opioid use (e.g., gastrointestinal side effects (e.g., inhibition of intestinal motility, GI sphincter constriction, constipation) nausea, emesis, (vomiting), dysphoria, pruritus, etc.) or a combination thereof inventive forms of Compound 1, or Compound 1 Compositions, and pharmaceutically acceptable compositions and formulations thereof, are useful for preparations of medicaments, useful in treatment of patients receiving acute opioid therapy (e.g., patients suffering from post-operative gastrointestinal dysfunction receiving acute opioid administration) or subjects using opioids chronically (e.g., terminally ill patients receiving opioid therapy such as an AIDS patient, a cancer patient, a cardiovascular patient; subjects receiving chronic opioid therapy for pain management; or subjects receiving opioid therapy for maintenance of opioid withdrawal). Still further, preparation of medicaments useful in the treatment of pain, treatment of inflammatory conditions such as inflammatory bowel syndrome, treatment of infectious diseases, treatment of diseases of the musculoskeletal system such as osteoporosis, arthritis, osteitis, periostitis, myopathies, treatment of autoimmune diseases and immune suppression, therapy of post-operative gastrointestinal dysfunction following abdominal surgery (e.g., colectomy (e.g., right hemicolectomy, left hemicolectomy, transverse hemicolectomy, colectomy takedown, low anterior resection), idiopathic constipation, and ileus (e.g., post-operative ileus, post-partum ileus), and treatment of disorders such as cancers involving angiogenesis, chronic inflammation and/or chronic pain, sickle cell anemia, vascular wounds, and retinopathy.

Still further encompassed by the invention are pharmaceutical packs and/or kits comprising an inventive form of Compound 1, or Compound 1 Composition, or a pharmaceutically acceptable composition or formulation thereof, and a container (e.g., a foil or plastic package, or other suitable container). Optionally instructions for use are additionally provided in such kits.

In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

All features of each of the aspects of the invention apply to all other aspects mutatis mutandis.

EXEMPLIFICATION

General Procedures

Compound 1 is prepared according to the methods described in detail in International Patent Application publication number WO2006/127899, the entirety of which is hereby incorporated herein by reference.

X-Ray Powder Diffraction (XRPD): X-ray powder diffraction (XRPD) analyses were performed using a Shimadzu XRD-6000 X-ray powder diffractometer using Cu Kα radiation. The instrument is equipped with a long fine focus X-ray tube. The tube voltage and amperage were set to 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1° and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A θ-2θ continuous scan at 3°/min (0.4 sec/0.02° step) from 2.5 to 40° 2θ was used. A silicon standard was analyzed to check the instrument alignment. Data were collected and analyzed using XRD-6100/7000 v. 5.0. Samples were prepared for analysis by placing them in an aluminum holder with silicon insert.

XRPD Pattern Analyses: X-ray powder diffraction (XRPD) analyses were performed using an Inel XRG-3000 diffractometer equipped with a CPS (Curved Position Sensitive) detector with a 2θ range of 120°. Real time data were collected using Cu-Kα radiation at a resolution of 0.03° 2θ. The tube voltage and amperage were set to 40 kV and 30 mA, respectively. The monochromator slit was set at 5 mm by 160 μm or at 2 mm by 160 μm. The pattern is displayed from 2.5-40° 2θ. Samples were prepared for analysis by packing them into thin-walled glass capillaries. Each capillary was mounted onto a goniometer head that is motorized to permit spinning of the capillary during data acquisition. The samples were analyzed for 5 min or 10 min. Instrument calibration was performed using a silicon reference standard.

XRPD Pattern Collection: XRPD patterns were collected with a Bruker D-8 Discover diffractometer and Bruker's General Area Diffraction Detection System (GADDS, v. 4.1.20). An incident beam of Cu Kα radiation was produced using a fine-focus tube (40 kV, 40 mA), a Göbel mirror, and a 0.5 mm double-pinhole collimator. A specimen of the sample was packed in a capillary and secured to a translation stage. A video camera and laser were used to position the area of interest to intersect the incident beam in transmission geometry. The incident beam was scanned to optimize orientation

statistics. A beam-stop was used to minimize air scatter from the incident beam at low angles. Diffraction patterns were collected using a Hi-Star area detector located 15 cm from the sample and processed using GADDS. The intensity in the GADDS image of the diffraction pattern was integrated using a step size of 0.04° 2θ. The integrated patterns display diffraction intensity as a function of 2θ. Prior to the analysis a silicon standard was analyzed to verify the Si 111 peak position. XRPD peak listings were generated using Pattern Match software, version 2.1.1.

Differential Scanning Calorimetry ("DSC"): Differential scanning calorimetry was performed using a TA Instruments differential scanning calorimeter 2920. The sample was placed into an aluminum DSC pan, and the weight accurately recorded. The pan was covered with a lid and left uncrimped. The sample cell was heated under a nitrogen purge at a rate of 10° C./min, up to a final temperature of 250 or 300° C. Indium metal was used as the calibration standard. Reported temperatures are at the transition maxima.

Thermogravimetry ("TG"): Thermogravimetric analyses were performed using a TA Instruments 2950 thermogravimetric analyzer. Each sample was placed in an aluminum sample pan and inserted into the TG furnace. The furnace was heated under nitrogen at a rate of 10° C./min, up to a final temperature of 350° C. Nickel and AlumelÔ were used as the calibration standards.

Solution 1D ^{1}H NMR Spectroscopy: The solution ^{1}H NMR spectra were acquired at ambient temperature with a Varian ^{UNITY}INOVA-400 spectrometer at a Larmor frequency of 399.796 MHz. The sample was dissolved in DMSO-d_6. The spectrum was acquired with a ^{1}H pulse width of 8.2 μs, a 2.50 second acquisition time, a 5 second delay between scans, a spectral width of 6400 Hz with 32000 data points, and 40 co-added scans. The free induction decay (FID) was processed using Varian VNMR 6.1C software with 131072 points and an exponential line broadening factor of 0.2 Hz to improve the signal-to-noise ratio. The residual peak from incompletely deuterated DMSO is at approximately 2.50 ppm. The relatively broad peak at approximately 3.3 ppm is due to water. The spectrum was referenced to internal tetramethylsilane (TMS) at 0.0 ppm.

Example 1

Preparation of Form A

Compound 1 (54.7 mg) was dissolved in 2,2,2-trifluoroethanol (2 mL), and the solution was filtered through a 0.2 μm nylon filter into a 20-mL vial. The 20-mL vial was placed inside a 100-mL glass jar containing 5 mL of ethyl acetate. The 20-mL vial was left uncapped and the jar was capped to allow vapor diffusion to occur. After four days, single crystals were observed in solution.

The monoclinic cell parameters and calculated volume at 150° K are: a=7.9013(3) Å, b=12.7337(9) Å, c=9.4247(7) Å, α=90.00°, β=98.868(4)°, γ=90.00°, V=936.91(10) Å^3, wherein each value is ±1.5. For Compound 1, Form A, the formula weight is 435.35 g/mol with Z=2 resulting in a calculated density is 1.543 g cm^{-3}. The space group was determined to be P21 (no. 4), this is a chiral space group. A single crystal of Form A of Compound 1 was indexed at room temperature and the unit cell parameters are summarized in Table 5, below.

TABLE 5

Unit Cell Data for Form A

	Form A 150° K Data	Form A RT Data
space group	$P2_1$ (No. 4)	$P2_1$ (No. 4)
a, Å	7.9013(3)	7.752(2)
b, Å	12.7337(9)	13.038(12)
c, Å	9.4247(7)	9.493(3)
α, deg	90	90
β, deg	98.868(4)	97.98(2)
γ, deg	90	90
V, Å^3	936.19(10)	945.7
Z	2	2
temp K	150	298

Example 2

Preparation of Form B

Compound 1 (52.8 mg) was dissolved in methanol (35 mL) with sonication to obtain a clear solution. The solution was filtered through a 0.2 μm nylon filter (Whatman) and evaporated using a rotary evaporator (ambient temperature bath used). The sample was left on the rotary evaporator for approximately 1 hour after the sample was visually dry. White solid containing birefringent spherulites of needles and blades resulted. XRPD pattern of Form A+peaks was observed when the evaporation was carried out at approx. 45° C.

Example 3

Preparation of Form C

Compound 1 (321.5 mg) was dissolved in TFE (4.28 mL) with sonication. A clear solution resulted. The solution was filtered through a 0.2 μM nylon filter (Whatman) into a clean 20-mL vial. A 500 μL aliquot of the filtered solution was dispensed into a 1-dram vial. Into this vial, aliquots (500 μL) of 1-propanol were dispensed with stirring until a total of 3 mL had been added. A clear solution resulted. The solution was allowed to stand at ambient conditions for approximately 1 hour. The sample was found to contain a very small amount of white precipitate suspended in solution. It was then placed in a refrigerator. A, clear solution containing colorless specks of solid resulted after 5 days. The solution was drawn off with a pipette and discarded, and the solid was allowed to air dry at ambient conditions overnight. The sample containing birefringent pentagonal plates was submitted for single crystal X-ray analysis.

The monoclinic cell parameters and calculated volume are: a=7.7724(6) Å, b=15.2539(6) Å, c=9.7329(6) Å, α=90.00°, β=91.899(3)°, γ=90.00°, V=1153.29(12) Å^3, wherein each value is ±1.5. For Compound 1 the formula weight is 496.45 g/mol with Z=2 the resulting calculated density of the crystal structure is 1.430 g cm^{-3}. The space group was determined to be P21 (no. 4), this is a chiral space group. The unit cell parameters for Form C are summarized in Table 6, below.

TABLE 6

Unit Cell Data for Form C

	Form C 150° K Data
space group	$P2_1$ (No. 4)
a, Å	7.7724(6)
b, Å	15.2539(6)
c, Å	9.7329(6)
b, deg	91.899(3)
V, $Å^3$	1153.29(12)
Z	2
crystal dimensions, mm	0.50 × 0.48 × 0.25
temp K	150

Example 4

Preparation of Form D

Amorphous Compound 1 was dissolved in methanol (concentration approximately 5 mg/mL) with sonication. A clear solution resulted. The solution was filtered through a 0.2 μm nylon filter (Whatman). Fast addition of ethyl acetate to a ratio of 4:1 ethyl acetate:methanol caused Form D to precipitate. The resulting white solid appeared to be non-birefringent and of unknown morphology. Experiments in which ethyl acetate was added more slowly to the same solvent ratio resulted in a clear solution. Slow evaporation of the solution resulted in white solid containing birefringent spherulites of thin needles. A fast evaporation experiment in which toluene replaced ethyl acetate also resulted in white solid containing large birefringent needles.

Example 5

Preparation of Amorphous Compound 1

Amorphous Compound 1 was prepared by lyophilization from an aqueous solution. A cycling DSC experiment was carried out on the amorphous Compound 1 and the glass transition temperature was determined to be approximately 23° C.

Example 6

Polymorph Screening of Compound 1

The forms of Compound 1, as described herein, were identified by a polymorph screen. In this screen, Compound 1 was subjected to a variety of solvents and conditions to effect crystallization or precipitation. The results of this screen are summarized in Tables 7 though 13, below. These Tables indicate the solvent and conditions utilized, the form obtained (as determined by XRPD), and a description of the crystal habit. In these Tables, the conditions are designated as slurry, FE, SC, FD, CP, RE, or SE. Each of these terms is defined in detail below.

As used herein, the term "Crash Precipitation" ("CP") refers to a method where saturated solutions of Compound 1 were prepared in various solvents and filtered through a 0.2-μm nylon filter into an open vial. Aliquots of various antisolvents were dispensed with stirring until precipitation occurred. In some cases, samples were placed in the refrigerator or freezer to facilitate precipitation. Solids were collected by drawing solvent off with a pipette and allowing the solids to air dry at ambient conditions prior to analysis.

As used herein, the term "Freeze Drying" ("FD") refers to a method where a saturated solution of Compound 1 was prepared in water and the solution was filtered through a 0.2-μm nylon filter into an open vial. The solution was frozen in a thin layer on the walls of the vial by rotating in a bath of liquid nitrogen or dry ice and washing isopropanol. The vial containing the frozen sample was placed into a lyophilizing container which was then attached to a Flexi-Dry lyophilizer for one to three days. The temperature was maintained at −50 to −60° C. for the duration of the experiment.

The term "Fast Evaporation" ("FE") refers to a method where solutions of Compound 1 were prepared in various solvents in which samples were sonicated between aliquot additions. Once a mixture reached complete dissolution, as judged by visual observation, the solution was filtered through a 0.2-μm nylon filter. The filtered solution was allowed to evaporate at ambient conditions in an open vial. The solids were isolated and analyzed.

The term "Rotary Evaporation" ("RE") refers to a method where concentrated solutions of Compound 1 or amorphous Compound 1 were prepared in various organic solvents and filtered through a 0.2-μm nylon filter into an open vial or flask. In some cases, 4-5 mL, aliquots of the filtered solution were dispensed into a clean vial. The vial was attached to a rotary evaporator and the solvent was evaporated to dryness. The water bath was at ambient temperature usually, but in some eases, the water bath was heated to approximately 50° C. to facilitate evaporation. If the sample was not completely dry after rotary evaporation, the vial was placed in a vacuum oven at 25° C. for 18 hours. The solids were isolated and analyzed.

As used herein, the term "Slow Cool" ("SC") refers to a method where saturated solutions of Compound 1 were prepared in various solvents at an elevated temperature and filtered warm through a 0.2-μm nylon filter into a warm vial. The vial was capped and left on the hot plate, and the hot plate was turned off to allow the sample to slow cool to ambient temperature.

The term "Slow Evaporation" ("SE") refers to a method where solutions of Compound 1 were prepared in various solvents in which samples were sonicated between aliquot additions. Once a mixture reached complete dissolution, as judged by visual observation, the solution was filtered through a 0.2-μm nylon filter. In some cases, aliquots of antisolvent were then added to the filtered solution with stirring. The solution was allowed to evaporate at ambient conditions in a vial covered with aluminum foil perforated with pinholes. The solids were isolated and analyzed.

The term "Slurry Experiments" refers to a method where suspensions of Compound 1 were prepared by adding enough solids to a given solvent at ambient conditions or elevated temperature so that undissolved solids were present. The mixture was then loaded onto an orbit shaker in a sealed vial at either ambient or elevated temperature for 7 days. The solids were isolated by vacuum filtration or by drawing the liquid phase off with a pipette and allowing the solids to air dry at ambient conditions prior to analysis.

As used herein, the term "Vapor Diffusion Experiments" refers to a method where concentrated solutions of Compound 1 were prepared in various solvents and filtered through a 0.2-μm nylon filter. The filtered solution was dispensed into a 1-dram vial, which was then placed inside a 20-mL vial containing approximately 2 mL of antisolvent. The 1-dram vial was left uncapped and the 20-mL vial was capped to allow vapor diffusion to occur. Solids were collected by vacuum filtration and analyzed.

The terra "Capillary Crystallization Techniques" refers to a method where a capillary polymorph screen was carried out

on Compound 1. Various crystallization techniques were employed. These techniques are described below, X-ray powder diffraction quality capillaries were used. Once solids were observed from the crystallization attempts, they were examined under a microscope for birefringence and morphology. Any crystalline shape was noted, but sometimes the solid exhibited unknown morphology, in some cases due to the packing in the capillary or to small particle size. When sufficient, solid samples were then analyzed by XRPD, and the crystalline patterns were compared to each other to identify new crystalline forms.

The term "CentriVap Crystallizations" ("CentriVap") refers to a method where a solution of Compound 1 in a given solvent or solvent mixture was prepared and filtered through a 0.2-μm nylon filter. A capillary was filled with 45 μL of solution via syringe. The capillary was centrifuged. The solvent was evaporated in a Labconco CentriVap® centrifugal evaporator under reduced pressure using a mechanical vacuum pump. The evaporator temperature was maintained at ambient temperature.

The term "Evaporation in Capillary" ("EC") refers to a method where a solution of Compound 1 in a given solvent or solvent mixture was prepared and filtered through a 0.2-μm nylon filter. A capillary was filled with 45 μL of solution via syringe. The capillary was centrifuged. Evaporations were performed in open capillaries at ambient and elevated temperature.

The term "Solvent/Antisolvent Crystallizations in Capillary" refers to a method where a solution of Compound 1 in a given solvent was prepared and filtered through a 0.2-μm nylon filter. A capillary was filled with 15 μL of solution and centrifuged. Then 30 μL of an antisolvent was added. The capillary was centrifuged. If a clear solution resulted, the capillary was left at ambient conditions to allow the solvents to evaporate, or evaporation was performed in a Labconco CentriVap centrifugal evaporator under reduced pressure using a mechanical pump at ambient conditions.

The term "Vapor Diffusion in Solid or Vapor Stress" ("VS") refers to a method where capillaries were packed with approximately 1 cm of Compound 1. The solids were exposed to solvent vapors by placing the capillaries in tall vials containing about 5 mL of various solvents. The capillaries were removed after approximately 14 days.

TABLE 7

Polymorph Screen of Compound 1

Solvent	Conditions	Habit/Description	XRPD Result
acetone	slurry, 7 days air-dried, 1 day	tiny white plates, birefringent	A
acetonitrile	slurry, 7 days air-dried, 1 day	white, morphology unknown, birefringent	A
2-butanone	slurry, 7 days air-dried, 1 day	white, morphology unknown, birefringent	A
t-butyl methyl ether	slurry, 7 days air-dried, 3 days	white blades, birefringent	A
methylene chloride	slurry, 7 days air-dried, 1 day	white, morphology unknown, birefringent	A
diisopropyl ether	slurry, 7 days air-dried, 1 day	white, morphology unknown, birefringent	A
1,4-dioxane	slurry, 7 days air-dried, 3 days	white plates, birefringent	A
ethanol	slurry, 4 days	clear solution	—
	FE, air-dried, 3 days	orange glassy film, not birefringent; morphology unknown, birefringent	amorphous
	SC	clear yellow solution	—
	SE	clear yellow solution	—
	RE	yellow glassy film, not birefringent; yellow, morphology unknown, birefringent	amorphous
ethyl acetate	slurry, 7 days air-dried, 3 days	white plates and blades, birefringent	A
heptane	slurry, 7 days air-dried, 3 days	white, morphology unknown, birefringent	A
hexafluoro-isopropanol	FE	clear glassy film, not birefringent	—
	SE	clear glassy film, not birefringent	—
	CP w/ acetonitrile	white, morphology unknown, birefringent	A
	CP w/ 2-butanone	white, morphology unknown, birefringent	A
	CP w/ isopropyl ether	white spherulites of needles and morphology unknown, birefringent	A
	CP w/ 1,4-dioxane	orange plates and morphology unknown, birefringent; morphology unknown, not birefringent	A minus one peak

TABLE 7-continued

Polymorph Screen of Compound 1

Solvent	Conditions	Habit/Description	XRPD Result
	CP w/ ethyl acetate	tiny white spherulites of blades, birefringent	A
	CP w/ isopropanol	white, morphology unknown, birefringent	amorphous
	CP w/ n-propanol	white blades, birefringent	A
	RE	white, bubbly solid	amorphous
isopropanol	slurry, 7 days	white plates and blades, birefringent	A
methanol	FE	tiny white blades, birefringent	A
	SE	amber-colored oily film, not birefringent; plates and morphology unknown, birefringent	A
	SC	clear solution	—
	RE	white spherulites of needles, birefringent	B
	RE (scale up)	white spherulites of needles and blades, birefringent	B
		white, morphology unknown, partially birefringent; fibers, birefringent	B
	RE at 45° C. to ambient	white, morphology unknown, partially birefringent	A + peaks
nitromethane	slurry, 7 days air-dried, 3 days	white, morphology unknown, birefringent	A
	FE (liquid phase from slurry 2454-01-12)	amber-colored, large pentagonal plates, birefringent	A
nitromethane: hexafluoro-isopropanol 10:1	SE	white cracked glass, birefringent	A
nitromethane: 2,2,2-trifluoroethanol 6:1	SE	white plates and dendridic needles, birefringent	A
1-propanol	slurry, 7 days air-dried, 3 days	white, morphology unknown, birefringent	A
tetrahydrofuran	slurry, 7 days air-dried, 3 days	white plates and blades, birefringent	A
toluene	slurry, 7 days air-dried, 3 days	white plates and blades	A
toluene: hexafluoro-isopropanol 10:1	SE	textured glassy film, not birefringent; off-white, morphology unknown, not birefringent; off-white needles, birefringent	A
toluene: 2,2,2-trifluoroethanol 6:1	SE	yellow translucent glassy film, not birefringent	—
2,2,2-trifluoroethanol	FE	clear glassy film, not birefringent	—
	SE	clear textured glassy film, not birefringent	—
	CP w/ acetonitrile	white plates, birefringent	A
	CP w/ 2-butanone	white blades, birefringent	A
	CP w/ 1,4-dioxane	white, morphology unknown, birefringent	A
	CP w/ ethyl acetate	white, morphology unknown, not birefringent	A
	CP w/ isopropanol	white needles and blades, birefringent	A

TABLE 7-continued

Polymorph Screen of Compound 1

Solvent	Conditions	Habit/Description	XRPD Result
	CP w/ n-propanol	white, pentagonal plates, birefringent	A + C
	RE	white, bubbly solid; dendridic needles, birefringent	amorphous
water	FE	yellow glassy film, not birefringent	—
	SE	light yellow glassy film, not birefringent	—
acetone:water 50:50	FE	clear glassy film, not birefringent	—
	SE	clear glassy film, not birefringent	—
acetone:water 99:1	slurry, 7 days	white plates and blades, birefringent	A
acetonitrile: water 80:20	FE	clear glassy film, not birefringent; colorless, morphology unknown, birefringent	amorphous
	SE	clear glassy film, not birefringent; colorless, morphology unknown, birefringent	amorphous
acetonitrile: water 99:1	slurry, 7 days	white plates and blades, birefringent	A
isopropanol: water 50:50	FE	clear glassy film, not birefringent	—
	SE	off-white, morphology unknown, birefringent	A
isopropanol: water 99:1	slurry, 7 days	tiny white plates, birefringent	A
acetone	slurry, 7 days	white, morphology unknown, birefringent	A
acetonitrile	slurry, 7 days	white, morphology unknown, birefringent	A
	FE (liquid phase from slurry 2454-20-02)	colorless textured glassy film, not birefringent	—
tetrahydrofuran	slurry, 7 days	white, morphology unknown, birefringent	A

TABLE 8

Vapor Diffusion Experiments

Solvent	Antisolvent	Time	Habit/Description	XRPD Result
hexafluoro-isopropanol	acetone	6 days	white, morphology unknown, birefringent	A
	dichloro-methane	14 days	clear solution	—
2,2,2-trifluoro-ethanol	acetone	10 days	translucent, morphology unknown, not birefringent; white plates, birefringent	A
	dichloro-methane	14 days	clear solution	—

TABLE 9

Capillary Polymorph Screen of Compound 1

Solvent	Method	Habit/Description	XRPD Result
hexafluoro-isopropanol	EC, ambient	clear solution	—
	EC, 40° C.	clear glassy solid, not birefringent	—

TABLE 9-continued

Capillary Polymorph Screen of Compound 1

Solvent	Method	Habit/Description	XRPD Result
	CentriVap	off-white solid, glassy, not birefringent and viscous liquid	—
2,2,2-trifluoro-ethanol	EC, ambient	off-white dendridic formations, birefringent	IS
	EC, 40° C.	clear yellow glassy solid, not birefringent	—
	CentriVap	off-white, morphology unknown, birefringent	A
water	EC, ambient	clear yellowish solution	—
	EC, 40° C.	clear yellow viscous liquid	—
	CentriVap	clear glassy, not birefringent	—
acetone: water 50:50	EC, ambient	clear yellowish solution	—
	EC, 40° C.	clear yellowish sticky substance	—
	CentriVap	off-white, morphology unknown, birefringent	A (small amount of material

TABLE 9-continued

Capillary Polymorph Screen of Compound 1

Solvent	Method	Habit/Description	XRPD Result
acetonitrile: water 50:50	EC, ambient	yellowish viscous liquid	—
	EC, 40° C.	clear yellow glassy solid, not birefringent	—
	CentriVap	off-white, morphology unknown, birefringent	A (small amount of material)
isopropanol: water 50:50	EC, ambient	clear yellowish solution	—
	EC, 40° C.	Clear orange glassy solid, not birefringent	—
	CentriVap	off-white, morphology unknown, birefringent	A

TABLE 10

Capillary Polymorph Screen of Compound 1 by Solvent/Antisolvent Crystallization

Solvent	Antisolvent	Method	Habit/Description	XRPD Result
HFIPA	acetonitrile	EC	Off-white plate, blades, and rods, birefringent	IS
	acetonitrile	CentriVap	clear and yellow glassy solid, not birefringent	—
	2-butanone	precipitation	clear glassy solid, not birefringent	—
	ethyl acetate	precipitation	white, morphology unknown, not birefringent	A
	isopropyl ether	precipitation	white, morphology unknown, not birefringent	A
	isopropanol	EC	Clear glassy solid, not birefringent	—
	isopropanol	CentriVap	clear glassy solid, not birefringent	—
	n-propanol	EC	clear viscous liquid	—
	n-propanol	CentriVap	clear and off-white glassy solid, not birefringent	—
	toluene	EC	clear yellowish viscous liquid	—
	toluene	CentriVap	clear and yellow glassy solid, not birefringent	—
	nitromethane	EC	off-white, unknown morphology, not birefringent and needles, birefringent	A
	nitromethane	CentriVap	clear and yellow glassy solid, not birefringent	—
TFE	acetonitrile	EC	clear sticky substance	—
	acetonitrile	CentriVap	off-white, dendridic formations, birefringent	A
	2-butanone	EC	clear viscous liquid	—
	2-butanone	CentriVap	white, dendridic formations, birefringent	A
	ethyl acetate	precipitation	white, morphology unknown, partially birefringent	A
	isopropyl ether	precipitation	white, morphology unknown, partially birefringent	A
	isopropanol	EC	yellowish viscous liquid	—

TABLE 10-continued

Capillary Polymorph Screen of Compound 1 by Solvent/Antisolvent Crystallization

Solvent	Antisolvent	Method	Habit/Description	XRPD Result
	isopropanol	CentriVap	off-white, dendridic formations, birefringent	A (big crystals present)
	n-propanol	EC	clear solution	—
	n-propanol	CentriVap	white, dendridic formations, birefringent	A
	toluene	EC	off-white, dendridic formations, birefringent	IS
	toluene	CentriVap	off-white, dendridic formations, birefringent	A
	nitromethane	EC	off-white, morphology unknown, not birefringent	IS
	nitromethane	CentriVap	clear glassy solid, not birefringent	—

TABLE 11

Capillary Polymorph Screen of Compound 1 by Vapor Stress

Solvent	Habit/Description	XRPD Result
acetone	white, morphology unknown, not birefringent	A
acetonitrile	white, morphology unknown, not birefringent	A
2-butanone (MEK)	white, morphology unknown, not birefringent	A
t-butyl methyl ether (MTBE)	white, morphology unknown, not birefringent	A
ethanol	white, morphology unknown, not birefringent	A
ethyl acetate	white, morphology unknown, not birefringent	A
isopropanol	white, morphology unknown, not birefringent	A
methanol	off-white, morphology unknown, not birefringent	B
toluene	white, morphology unknown, not birefringent	A
95% RH	white, morphology unknown, not birefringent	A

TABLE 12

Abbreviated Polymorph Screen of Amorphous Compound 1

Solvent	Conditions	Habit/Description	XRPD Result
acetone	slurry, 7 days	white, morphology unknown, birefringent	A

TABLE 12-continued

Abbreviated Polymorph Screen of Amorphous Compound 1

Solvent	Conditions	Habit/Description	XRPD Result
acetonitrile	slurry, 7 days	white, morphology unknown, birefringent	A, minus one peak
acetonitrile: hexafluoro-isopropanol 9:1	FE	clear glassy film, not birefringent; clear, morphology unknown, birefringent	A, l.c.
acetonitrile: methanol 4:1	SE	clear solution	—
	FE	yellow glassy film, not birefringent	—
2-butanone	slurry, 7 days	white, tiny plates, birefringent	A
2-butanone: hexafluoro-isopropanol 9:1	FE	clear glassy film, not birefringent; clear plates and morphology unknown, birefringent	IS
2-butanone: methanol 4:1	SE	clear light yellow solution	—
	FE	clear oily film, not birefringent; colorless needles and blades, birefringent	IS
ethanol	FE	clear glassy film, not birefringent; colorless, morphology unknown, birefringent	amorphous
	RE	white, morphology unknown, not birefringent	amorphous
ethyl acetate	slurry, 7 days	white, morphology unknown, birefringent	A, minus one peak
ethyl acetate: methanol 4:1	SE	white spherulites of thin needles, birefringent	D
	SE, scale-up	yellow needles, birefringent	D + B
		long needles, single crystal quality	B
		a few needles + colorless thin solid film	—
	2410-52-01 + solvent mixture	long needles	—
	SE, scale-up	clear solution	—
	SE, scale-up	clear solution	—
	SE, scale-up	white, long needles	—
	Portion of 2482-09-03	white, long needles, birefringent	B
	SE, scale-up	needles	—
hexafluoro-isopropanol	FE	clear glassy film, not birefringent	—
	CP w/ acetonitrile	clear solution with small amount of translucent solid	—
	CP w/ 2-butanone	clear solution with small amount of translucent solid	—
	CP w/ ethyl acetate	white blades, birefringent	A
	CP w/ isopropanol	clear solution, very small amount of translucent solid	—
isopropanol	slurry, 7 days	white plates and blades, birefringent; morphology unknown, not birefringent	A
isopropanol: hexafluoro-isopropanol 9:1	SE	clear glassy film, not birefringent; colorless, morphology unknown, birefringent	IS
isopropanol: methanol 4:1	SE	clear light yellow solution	—
	FE	orange glassy film, not birefringent; colorless, morphology unknown, birefringent	A, l.c.
isopropyl ether	slurry, 7 days	white, morphology unknown, not birefringent	A
methanol	FE	clear glassy film, not birefringent; colorless, morphology unknown, birefringent	amorphous
	RE	white, cracked glassy film, not birefringent	amorphous
	CP w/ isopropyl ether	white, morphology unknown, not birefringent	B + A
	CP w/ ethyl acetate	white, morphology unknown, not birefringent	D
		white precipitate	D
		white, morphology unknown, not birefringent	B
		white, thin needles, partially birefringent	B minus peaks
		white, morphology unknown, partially birefringent	B minus peaks
		white, morphology unknown, partially birefringent	B minus peaks
		white solid	D + B minus peaks
		white solid	D + B minus peaks
nitromethane	FE	clear glassy film, not birefringent; white blades, birefringent	A
tetrahydro-furan	slurry, 7 days	off-white, morphology unknown, birefringent	A
toluene	slurry, 7 days	white, morphology unknown, not birefringent	A
toluene: hexafluoro-isopropanol 9:1	SE	clear solution	—
	FE	translucent glassy film, not birefringent; orange, morphology unknown, not birefringent	amorphous
toluene: methanol 4:1	SE	clear solution, small amount of white needles and yellow oil	—
	FE	yellow glassy film, not birefringent; white, large needles, birefringent	D
2,2,2-trifluoroethanol	FE	translucent glassy film, not birefringent	—
water	FE	light yellow cracked glassy film, not birefringent; light yellow fibers, birefringent	IS
acetone:water 99:1	slurry, 7 days	white, morphology unknown, not birefringent	A
acetonitrile: water 99:1	slurry, 7 days	white needles and morphology unknown, birefringent; morphology unknown, partially birefringent	A
isopropanol: water 99:1	slurry, 7 days	white, morphology unknown, partially birefringent	A

TABLE 13

Vapor Diffusion Experiments on Amorphous Compound 1

Solvent	Antisolvent	Time	Habit/Description	XRPD Result
hexafluoro-isopropanol	acetone	11 days	white, morphology unknown, partially birefringent	IS
	tetrahydrofuran	7 days	white, morphology unknown, not birefringent	—
2.2,2-trifluoro-ethanol	acetone	11 days	white, morphology unknown, birefringent	IS
	tetrahydrofuran	7 days	white, morphology unknown, not birefringent	A

Example 7

Equilibrium solubilities of Form A in various solvents at room temperature are listed in Table 14, below. In each case, the equilibrium solubility of Form A at room temperature was measured by placing the compound in excess into different solvents and stirring overnight at ambient room temperature, protected from light. Solubility in the following solvents and aqueous buffers was evaluated at room temperature: methanol, ethanol, benzyl alcohol, dimethyl sulfoxide, water for injection, bacteriostatic water (containing 0.9% benzyl alcohol), 5% dextrose, normal saline (0.9% NaCl), pH 1.1 (glycine HCl), pH 4.2 (glycine HCl), pH 7.1 (phosphate buffer), and pH 9.1 (glycine). Solubilities are reported to the nearest mg/mL unless otherwise stated.

An additional set of solubility samples, were prepared under conditions that simulate the human GI tract (pH 1, 0.1 N HCl, pH 4.5 acetate buffer, 7.1 phosphate buffer, pH 9.0 borate buffer). All solutions were stored overnight in a 37° C. oven, and then filtered through a Whatman 0.45 μm nylon syringe filter to remove insoluble material. The filtrate was analyzed by HPLC for strength and the results summarized in Table 14.

TABLE 14

Approximate Solubilities of Form A, at Ambient Temperature

Solvent	Solubility at R.T. (mg/mL)	Solubility at 37° C. (mg/mL)
Methanol	2.5	N/T
Ethanol	6.1	N/T
Benzyl alcohol	85.5	N/T
Dimethylsulfoxide	>170	N/T
Water for injection	73.5	N/T
Bacteriostatic water (0.9% benzyl alcohol)	86.5	N/T
5% Dextrose	61.3	N/T
Normal saline (0.9% NaCl)	59.7	N/T
0.1N HCl	76.6	100.8
pH 1.1 (glycine HCl buffer)	70.1	N/T
pH 4.2 (glycine HCl buffer)	73.8	N/T
pH 4.5 (acetate buffer)	N/T	99.97
pH 7.1 (phosphate buffer)	74.9	N/T

TABLE 14-continued

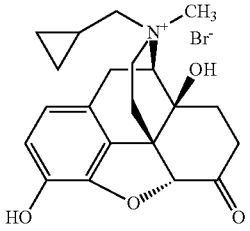
Approximate Solubilities of Form A, at Ambient Temperature

Solvent	Solubility at R.T. (mg/mL)	Solubility at 37° C. (mg/mL)
pH 9.1 (glycine buffer)	71.1	N/T
pH 9.0 (borate buffer)	N/T	100.6
pH 6.8 (phosphate buffer)	N/T	100.7

N/T = "not tested"

We claim:

1. Form D of Compound 1:



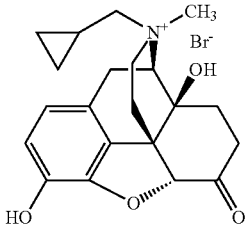
1

where the compound is in the (R) configuration with respect to the nitrogen, and wherein the compound has an X-ray powder diffraction pattern comprising all of the peaks at about 7.66, 8.42, 14.79, and 21.06 degrees 2-theta.

2. Form D of Compound 1 according to claim **1**, wherein the X-ray powder diffraction pattern further comprises peaks at about 12.85, 13.48, 16.11, 17.53, 18.67, 19.61, 21.79, 22.07, 23.25, 24.53, and 26.23 degrees 2-theta.

3. Form D of Compound 1 according to claim **1**, characterized in that the compound has an X-ray powder diffraction pattern substantially similar to that depicted in FIG. **6**.

4. Form C of Compound 1:



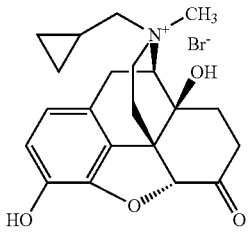
1

where the compound is in the (R) configuration with respect to the nitrogen, and wherein the compound has an X-ray powder diffraction pattern, calculated from single crystal data collected at a temperature of 150±1° K, comprising all of the peaks at about 10.8, 12.8, 14.8, 15.9, 16.25, 18.5, 19.15, 22, 23.6, 24.25, 25.7, 27.5, 28.1, 28.9, 31.5 and 31.75 degrees 2-theta.

5. Form C of Compound 1 according to claim **4**, characterized in that the compound has an X-ray powder diffraction pattern, calculated from single crystal data collected at a temperature of 150±1° K, substantially similar to that depicted in FIG. **8**.

6. Form C of Compound 1 according to claim **4**, wherein the compound has monoclinic cell parameters of: a=7.7724 (6) Å, b=15.2539(6) Å, c=9.7329(6) Å, α=90.00°, β=91.899 (3°), γ=90.00°, wherein each value is ±1.5 Å.

7. A composition comprising a mixture of Form A of Compound 1 and Form C of Compound 1:



where the compound is in the (R) configuration with respect to the nitrogen, and wherein the composition has an X-ray powder diffraction pattern comprising all of the peaks at about 10.58, 11.56, 13.88, 15.42, 20.82, 21.86, 22.74, 23.2, 24.74, and 26.96 degrees 2-theta.

8. The composition according to claim **7**, characterized in that the composition has a X-ray powder diffraction pattern substantially similar to that depicted in FIG. **9**.

9. A composition comprising Form D of Compound 1 of claim **1**.

10. A composition comprising Form C of Compound 1 of claim **4**.

11. A pharmaceutical composition comprising the composition of any one of claims **7**, **9** or **10**, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

12. An oral formulation comprising the pharmaceutical composition according to claim **11**.

13. A method of reducing a side effect of opioid therapy in a subject receiving opioid treatment comprising administering to the subject the pharmaceutical composition according to claim **11**.

14. A method for reducing an effect of endogenous opioid activity in a subject comprising administering to the subject the pharmaceutical composition according to claim **11**.

* * * * *